Cancer in the elderly

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Marjan de Rijke

The studies in this thesis were performed at the Comprehensive Cancer Centre Limburg (IKL) at the Department of Cancer Registration and Epidemiology.

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Er is nog zomer en genoeg,
Wat zou het loodzwaar tillen zijn
wat een gezwoeg
Als iedereen niet iedereen ter wille was,
Als iedereen niet
iedereen op handen droeg

Judith Herzberg

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1 Introduction

Background

At the end of the 1980s and the beginning of the 1990s, a lack of information regarding appropriate treatment for elderly cancer patients was already apparent [1]. One of the problems recognized was that knowledge of treatment methods was mainly based on experience with patients of younger than 70 years, because elderly patients were excluded from clinical trials [2]. Several authors reported differences in treatment by age for common forms of cancer [3-6]. A significant effect of age was described on the treatment for breast cancer, prostate cancer and lung cancer. Some studies also addressed the question of whether there were differences in survival between age groups. In the case of ovarian cancer, older patients appeared to have poorer survival, also when stage was taken into account [7,8]. A Dutch study on a large non-selected population of breast cancer patients found differences in treatment, but not in survival [9].
In 1995, as part of the annual report, the Regional Cancer Registry Maastricht, which is kept by the Comprehensive Cancer Centre Limburg (IKL), highlighted some forms of cancer including ovarian cancer. It appeared that remarkable age-specific differences existed in treatment for women with this form of cancer [10].

This all took place in a period in which the population of the Netherlands, like in many other Western countries, was ageing rapidly. In the period 1950-1998, the number of Dutch persons aged 75 years and older increased from 0.2 million to 0.9 million; also the number of persons aged 65-74 years doubled from 0.5 to 1.2 million. The expectations for the future are that the number of persons aged 65 years and older will continue to increase to a maximum of almost 24% of the total population around the year 2040; this percentage was 13.5% in 1998 [11]. Cancer is predominantly a disease of the elderly: at present, 45% of all incident cancer patients in the Netherlands are older than 70 years at diagnosis [12]. As an illustration of the increase in cancer patients as a result of ageing of the population alone (assuming that incidence rates remain the same) figure 1 presents the predicted numbers of invasive tumours for the years 2010, 2025 and 2040, with 1995 as the year of reference. The number of incident cancers among persons aged 75-84 years is projected to increase from 14731 in 1995 to 36354 in 2040 (147%). In persons aged 85 years and older, the number is projected to increase from 4042 in 1995 to 12247 in 2040, which is a proportional increase of 203%.

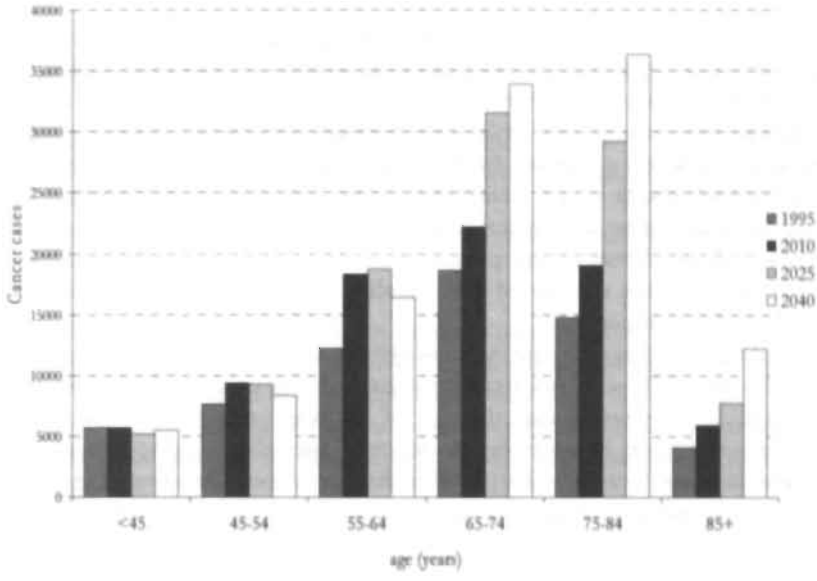

Figure 1 Number of invasive tumours in the total Dutch population according to age, observed in the year 1995 and predicted for the years 2010, 2025, 2040
Source: Netherlands Cancer Registry and Statistics Netherlands; expected numbers were calculated using the age-specific incidence rates of 1995 as reference

Healthy Dutch women at the age of 70 years have a mean life expectancy of 15 years, while for men this is almost 12 years (Table 1).
It is obvious that society will continue to be confronted with the burden of cancer in an increasing proportion of the population, which makes the problem of treating elderly patients with malignant disease more and more relevant.

Table 1 Mean life expectancy in the Netherlands by age for males and females

From age	Mean life expectancy in years	
	Males	**Females**
0 years	75	80
50 years	27	32
65 years	15	19
70 years	12	15
75 years	8	11
80 years	6	8
85 years	5	6
90 years	3	4
95 years	2	3
100 years	1.5	2

Source: Voorburg, Statistics Netherlands, 2002

Who are the elderly?

In this thesis, more than once it is stated that ageing is an individual process that cannot be defined by chronological or calendar age [13]. In analyses that examined age, however, categorical variables have been defined by using calendar age at the time of diagnosis.
Obviously, the definition of 'old' or 'elderly' depends very much on the context of where one stands. In the world of sports, for example, a gymnast of 18 years is almost ancient, whereas a football player is not considered to be old until he has reached his thirties. Special glossy magazines are directed at the 50^{+} group whereas for various social, economic and medical entitlement programmes 65 years is the traditional age of entry. Currently, even reaching the age of one hundred years, no longer automatically means your picture in the newspaper.
In health and medical research, the calendar ages of 70 and 85 years have special meaning. Especially the age of 70 years is a frequently used cut-off point in the literature on cancer in the elderly. It is assumed that the age of 70 years may well be the chronological beginning of senescence, because the incidence of age-related changes, such as a decline of vision and hearing, increases sharply after this age. Along the same lines, the age of 85 years may be considered as the beginning of frailty, a condition in which functional reserves have practically been exhausted [14].
Owing to the wide heterogeneity within the growing population of older people it has been proposed to refer to elderly people as the young-elderly (70-74 years), the older-elderly (75-84 years) and the very elderly persons (85^{+})[15].

Cancer registry data

Clinical studies, often based on hospital data registries, have the disadvantage that selection bias due to referral policies cannot be excluded. This problem can be avoided by using data from a population-based registry, i.e. a systematic collection of data on all malignant neoplasms occurring in a geographically defined population. All the studies presented in this thesis are based on data collected by the Maastricht Cancer Registry, kept by the Comprehensive Cancer Centre Limburg (IKL). In two studies data were also used from other regional cancer registries and in one study data were provided by the Netherlands Cancer Registry that covers the whole country.
In the Netherlands, cancer data have been recorded since the end of the 1980s at nine regional cancer registries. All data collected by the regional registries are submitted to the Netherlands Cancer Registry and stored in a national data bank. Completeness of the registry is high: more than 95% of all malignancies are recorded [16]. All regional cancer registries collect data according to a minimum data set, which includes identification information and tumour information. Coding of the items is based on international coding rules to facilitate international comparisons of cancer data.
For more information on the regions and registration procedures, the reader is refered to Schouten et al [17], Parkin [18] and Van der Sanden et al [19].

Aims and outline of the thesis

Cancer in the elderly is a very broad subject. This thesis concentrates on several aspects connected to this field of interest. Two objectives form the starting point:

1. Gaining insight into differences in diagnostics, treatment and survival between younger and older cancer patients and identifying underlying explanations for these differences.
2. Gaining insight into cancer incidence and cancer mortality in the very elderly population.

The age-specific variation in treatment for ovarian cancer patients, which was revealed in the annual report of the cancer registry in 1995, and the increasing interest of physicians in cancer in the elderly gave rise to the study described in **chapter 2**. This study concentrated on the differences in diagnostics and treatment between younger and older cancer patients with breast, colorectal, lung, ovarian, head and neck cancer and non-Hodgkin lymphoma.
To perform analyses on age-specific differences in survival, a form of cancer with a poor prognosis (ovarian cancer) and a form of cancer with a fairly good prognosis (cervical cancer) were chosen. Moreover, it was important to have a relatively small backlog when completing follow-up data on vital status **(chapters 3 and 4)**.
Large differences in treatment for lung cancer between age groups were found in the first study and the acknowledgement of the lack of information about important prognostic factors, such as comorbidity and performance status, formed the background for the study described in **chapter 5**. Thus the influence of underlying factors for age-specific differences in treatment choice, such as comorbidity and performance status, was examined in patients with non-small cell lung cancer. Then **chapter 6** addressed the cancer incidence and cancer mortality rates in people aged 85 years and older. Cancer incidence rate and mortality studies often present numbers and rates for elderly patients aged 70^+ years or 75^+ years, and sometimes even 65^+ years. The main reason for this is small numbers or unavailability of more detailed data. The increasing number of very elderly people has created the opportunity to divide cancer incidence and mortality rates into distinct age categories, even in patients aged 85-94 years and in patients aged ≥ 95 years.
In **chapter 7**, the results of the studies described in chapters 2-6 are discussed and recommendations are made for further research.

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2

Age-specific differences in the diagnostics and treatment of cancer patients aged 50 years and older in the province of Limburg, the Netherlands

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Summary

Background: In the Netherlands, 45% of all cancer cases occur in men and women aged 70 years and older. Since the population is ageing and cancer incidence rises with age, the number of new malignancies in the elderly is increasing. It has become apparent that there is a relationship between age at diagnosis and the treatment received. Therefore, age-specific variations in patterns of care for six common forms of cancer in the elderly, are examined.
Patients and Methods: Patients aged 50 years and older, diagnosed in the period 1988-1992 in Middle and South Limburg with breast, colorectal, lung, ovarian, head and neck cancer and non-Hodgkin lymphoma were included (N=6911). Data were obtained from the population-based Regional Cancer Registry of the Comprehensive Cancer Centre Limburg. Age-specific differences in diagnostics and treatment were analysed using chi-square analysis (age categories: 50-59, 60-69, 70+). Logistic regression analyses were used to examine the extent to which age increased the chance of not being treated or of receiving less intensive treatment, while controlling for the stage of the disease and the sex of the patient.
Results: For all malignancies the stage was unknown in a larger proportion of the patients aged 70 years and older than in the younger patient groups. Compared to their younger counterparts, the diagnosis of elderly breast, colorectal and lung cancer patients was more often based solely on clinical grounds. In the total study population, 16% were not treated. Per age category 50-59 years, 60-69 years and 70+ these percentages were 7%, 12% and 22% respectively (P-trend=0.001). For all malignancies the chance of not receiving treatment increased with increasing age. However, the size and nature of the differences varied with the localisation of the tumour. The proportion of untreated patients was particularly high in the patients with lung cancer and metastatic colorectal and ovarian cancer, and there was an increase with increasing age (P-trend=0.001). The vast majority of patients with NHL, breast, head and neck and non-metastatic colorectal cancer received treatment, 90%, 94%, 91%, and 99% respectively. However, elderly patients less often received a combination of treatment modalities.
Conclusions: The diagnostics and choice of treatment for several common types of cancer were dependent on age. This study could not take into account the major problem of comorbidity which can be a reason to choose for lesser therapy in the elderly. More research is necessary to determine which factors determine the diagnostics and choice of treatment and whether these factors differ between young and elderly patients.

Introduction

Steady increases in the survival length of cancer patients and of life expectancy as such in the Netherlands are expected to lead to an increase in the prevalence of cancer. At present, over 45% of incident cancer patients in the Netherlands are older than 70 years at diagnosis [1]. Very little knowledge is available on the course of disease in the elderly, or more importantly, on specific treatment policies for elderly cancer patients. Knowledge about treatment methods is mainly based on experience with patients younger than 70 years. Clinical trials often apply the same age limit [2,3]. In the few studies that included elderly patients, they were selected on the grounds of not having any comorbid conditions.

Existing literature gives the impression that a greater proportion of elderly patients are not treated or receive less intensive treatment (e.g. in terms of monotherapy versus combination therapy) than younger patients [4-11]. In addition, there is hesitance about administering chemotherapy to elderly patients and, not infrequently, a potentially curative operation is not performed because the risk is assumed to be too high [12-15]. It is not the elderly patients themselves who choose less intensive treatment, although for them toxicity and quality of life do weigh more heavily [16]. A survey by telephone revealed that treating physicians were less inclined to offer alternative treatment modalities to elderly patients [17].

We performed a study on the differences in diagnostics and treatment between young and elderly cancer patients in the Middle and Southern part of the province of Limburg. The study group comprised patients with several common forms of cancer: breast, colorectal, lung, ovarian, head and neck cancer and non-Hodgkin lymphoma. Besides the high incidence of these common tumours, variation in treatment modalities was a basis for selection.

Patients and methods

Data collection

Data on incident cancer cases and data on diagnostic procedures and treatment were obtained from the Regional Cancer Registry Limburg, a department of the Comprehensive Cancer Centre Limburg (IKL). This population-based Cancer Registry covers the regions of Middle and South Limburg with about 850,000 inhabitants and 8 hospitals (for a description of the region and registration procedures see [18]).

Study population

Patients aged 50 years and older who were diagnosed between 1 January 1988 and 31 December 1992 with breast cancer (n=1637), colorectal cancer (n=1935), lung cancer (n=2341), ovarian cancer (n=255), head and neck cancer (n=412) or a non-Hodgkin lymphoma (n= 331) were included in the study (total n=6911). We excluded patients who had had an earlier malignancy and those in whom the diagnosis had not been made until autopsy.

Definitions and operationalisation

Age
The patients were divided into three age categories: 50-59 years, 60-69 years and 70 years and older.

Tumour stage
In the IKL-registry tumour stage is registered according to the TNM classification system, the Ann Arbor staging system for lymphomas and the FIGO classification system for gynaecological tumours [19]. Tumour stage referred to the extent of the disease at the time of making the definitive decision about the treatment policy. For the current study, the simplified staging system was used: stage 1, 2, 3, or 4 and stage unknown. For the analysis of treatment by age, various stages were grouped together on the basis of similarities in general treatment modalities (see Table 1).

Grade of malignancy
Owing to the fact that in non-Hodgkin lymphoma more than in any other malignancy, classification according to malignancy grade plays a major role in determining the choice of treatment and the prognosis [20], this factor was also included in the analysis.

Diagnostics
The extent of the diagnostic work-up was derived from the basis for diagnosis and from the degree of certainty about the TNM classification (certainty factor). The basis for making the diagnosis was clinical (anamnesis and physical examination), cytological or histological; the latter was considered to be the most valid. The certainty factor is a measure of the extent and reliability of the examination procedures used for staging [19]. If there were insufficient data on the tumour (T), regional lymph nodes (N) or distant metastases (M) in the medical file that part of the TNM was coded C0. The certainty factor was recorded as C1 when data were available from standard examination procedures (anamnesis, X-ray photographs), C2 when data were available from more advanced examination procedures and C3 if surgical exploration had taken place. Per type of cancer (except for non-Hodgkin lymphomas because no C factor was recorded for them) we determined the proportion of patients per age category in whom the stage could be determined but for whom one or more parts of the TNM had a certainty factor of 0 (C0).

Treatment
Treatment concerned the primary treatment received by the patient in the first three months after diagnosis, in terms of: surgery, radiotherapy, chemotherapy, endocrine treatment, other therapy, all possible combinations of these, and no treatment. Treatment policies for patients with lung cancer were analysed separately for small-cell lung cancer and non-small cell lung cancer patients. Because the distinction between small cell and non-small cell lung cancer is based on the microscopically confirmed morphology of the tumour, the basis for diagnosis was not analysed separately in order to avoid the risk of selection bias.

An overview of regular treatment policies for the various malignancies in the IKL-region was made by two clinical consultants from the Comprehensive Cancer Centre Limburg (HS, JJ), an internist-oncologist and a radiotherapist-oncologist (see Table 1).

Table 1 General treatment per malignancy and stage in Middle and South Limburg

Malignancy	Stage	Treatment
Colorectal	I, II, III	Surgery whether or not in combination with radiotherapy or chemotherapy
	IV	Chemotherapy or no treatment
Lung, non-small cell	I, II, III	Surgery or radiotherapy or a combination of the two
	IV	No treatment
Lung, small cell	Limited	Chemotherapy whether or not in combination with surgery or radiotherapy
	Extensive	Chemotherapy
Breast	I, II, III	Surgery whether or not in combination with radiotherapy or chemotherapy or endocrine therapy
	IV	Chemotherapy or endocrine therapy
Ovary	I, II, III	Surgery in combination with chemotherapy
	IV	Chemotherapy
Head-neck	I, II, III	Surgery or radiotherapy or a combination of the two
	IV	Chemotherapy or no treatment
NHL-low grade	I	Radiotherapy
	II, III, IV	Chemotherapy whether or not in combination with radiotherapy
NHL-intermediate/high-grade	All	Chemotherapy whether or not in combination with radiotherapy

Data analysis

For each malignancy we analysed the relationship between age and the extent of the diagnostic work-up, and between age and treatment by using the Pearson Chi-square test and the Mantel-Haenszel chi-square test for trend. As the treatment for cancer depends on the extent of the tumour, for each malignancy we also analysed the relationship between tumour stage and the age category of the patient. With the aid of models based on logistic regression (SAS, procedure LOGIST) we evaluated the extent to which the age at diagnosis of each malignancy influenced the chance of not receiving treatment. These analyses were corrected for the effects of stage and sex.

Results

General

The total study population comprised 6911 patients (3515 men and 3396 women). The percentages of men in the lung cancer group, the head and neck tumour group, the non-Hodgkin lymphoma group and the colorectal tumour group were 91%, 79%, 48% and 49%, respectively.

Diagnosis

The diagnosis was confirmed histologically in 88% of the total patient population. Per age category 50-59 years, 60-69 years and 70+ these percentages were 93%, 90% and 83%, respectively. In the patients with breast, lung and colorectal cancer there was a significant increase in the proportion of patients without histological or cytological confirmation with increasing age, but proportions were very small. For ovarian cancer, 14% of the diagnosis of elderly patients was based on cytological grounds, while this was only 2% in the younger age categories. Also for lung cancer, cytological confirmation of the diagnosis played a fairly major role. In 20% of these patients the diagnosis was confirmed cytologically (see Table 3). In the three age categories 50-59 years, 60-69 years and 70+ years, the diagnosis was confirmed cytologically in 16%, 17% and 24%, respectively (P-trend=0.001).

Stage

Classification of tumour stage per age category is shown in Tables 2, 3 and 4. For all malignancies, the stage was unknown in a larger proportion of the elderly patients than the younger patients. The difference was statistically significant in all the malignancy groups, except for non-Hodgkin lymphoma and ovarian cancer (the two smallest groups). In the colorectal and lung tumour groups, this was associated with a lower proportion of elderly patients with more advanced stage disease, whereas in the breast and ovarian cancer groups, the proportion of women with stage 4 disease increased with increasing age. Furthermore, a relatively large number of young patients with advanced stage head and neck cancer was found: 41% in the 50-59 year olds versus 26% and 24% in the two other age categories. This was also true for colorectal cancer, 25%, 19% and 17%, respectively. When the proportion of unknown stages was added, this difference tended to disappear for the colorectal group but only partially disappeared for the head and neck cancer group.
Sometimes the stage of the disease was based on less extensive staging examinations (certainty factor=0 for T, N or M). This phenomenon was associated with increasing age, although this was not statistically significant (see Tables 2 and 3).

Table 2 Distribution according to age, stage, diagnostics and treatment for patients of 50 years and older with head and neck, breast, colorectal and ovarian cancer; IKL 1988-1992

	Head-Neck				Breast				Colorectal				Ovary			
Age (yrs)	50-59	60-69	70+	Total	50-59	60-69	70+	Total	50-59	60-69	70+	Total	50-59	60-69	70+	Total
N	111	163	138	412	488	552	597	1637	293	600	1042	1935	54	90	111	255
Stage																
I	25%	32%	36%	31%	36%	35%	19%	29%	22%	25%	3%	23%	24%	24%	18%	22%
II	12%	15%	9%	12%	47%	48%	49%	48%	25%	28%	28%	28%	17%	12%	9%	12%
III	9%	16%	10%	12%	10%	9%	14%	11%	25%	23%	22%	22%	46%	39%	40%	41%
IV	41%	26%	24%	30%	6%	6%	9%	7%	25%	19%	17%	19%	11%	20%	21%	18%
Unknown	12%	10%	22%	15%	2%	2%	9%	5%	3%	5%	11%	8%	2%	4%	9%	5%
Basis for diagnosis																
Histology	100%	99%	99%	99%	98%	98%	87%	94%	99%	97%	96%	97%	96%	97%	82%	90%
Cytology	-	1%	1%	1%	1%	1%	10%	5%	-	1%	1%	1%	2%	2%	14%	7%
Staging diagnostics insufficient[a]	6%	4%	10%	6%	3%	3%	4%	4%	4%	5%	6%	5%	6%	16%	18%	14%
Treatment Stage I-III	N 51	103	75	229	450	507	491	1448	209	454	754	1417	47	68	74	189
No treatment	2%	3%	7%	4%	-	-	1%	0%	2%	1%	1%	1%	2%	7%	13%	8%
Surgery (S)	29%	22%	21%	24%	17%	20%	30%	23%	81%	86%	90%	87%	19%	22%	24%	22%
Radiotherapy (RT)	49%	55%	52%	53%	-	0%	0%	0%	0%	1%	1%	1%	-	-	-	-
Chemotherapy (CT)	-	-	-	-	0%	0%	-	0%	1%	-	-	0%	11%	13%	19%	15%
Endocrine th.(ET)	-	-	-	-	1%	1%	14%	5%	-	-	-	-	-	-	-	-
S+RT	16%	15%	17%	16%	37%	38%	16%	31%	6%	4%	4%	4%	2%	1%	-	1%
S+CT	-	-	-	-	7%	3%	2%	4%	8%	6%	2%	4%	66%	54%	42%	52%
S+ET	-	-	-	-	12%	12%	27%	17%	-	-	0%	0%	-	-	-	-
Other	4%	4%	3%	3%	25%	25%	10%	20%	2%	2%	2%	3%	-	3%	2%	2%
Treatment Stage IV	N 46	43	33	122	27	34	51	112	74	115	178	367	6	18	23	47
No treatment	6%	9%	12%	9%	-	3%	12%	6%	8%	17%	30%	22%	-	40%	26%	28%
Surgery (S)	9%	7%	9%	8%	-	-	-	-	40%	48%	54%	50%	17%	6%	9%	8%
Chemotherapy (CT)	4%	-	3%	2%	18%	15%	4%	11%	11%	10%	4%	8%	33%	16%	52%	36%
Radiotherapy (RT)	33%	26%	33%	30%	-	-	2%	1%	1%	-	2%	1%	-	-	-	-
Endocrine th.(ET)	-	-	-	-	26%	35%	59%	44%	-	-	-	-	-	-	-	-
S+RT/ET/CT[b]	39%	51%	36%	43%	33%	23%	12%	20%	35%	20%	6%	16%	50%	38%	13%	28%
Other	9%	7%	7%	8%	23%	27%	11%	18%	5%	5%	4%	3%	-	-	-	-
Treatment Stage X	N 14	17	30	61	11	11	55	77	10	31	110	151	1	4	14	19
No Treatment	7%	-	13%	8%	9%	9%	16%	14%	30%	42%	61%	55%	100%	25%	50%	47%
Treatment	64%	77%	77%	74%	91%	82%	68%	73%	50%	45%	17%	32%	-	75%	36%	43%
Treatment ?	29%	23%	10%	18%	-	9%	16%	13%	20%	13%	12%	13%	-	-	14%	10%

[a] Thoroughness of staging diagnostics, derived from the certainty factor; these percentages are only valid for the patients with a known stage
[b] S+RT for head and neck cancer; S+ET for breast cancer; S+CT for ovary and colorectal cancer

Table 4 Distribution according to age, stage, diagnostics and treatment for patients of 50 years and older with a non-Hodgkin lymphoma; IKL, 1988-1992

		Non-Hodgkin Lymphoma			
Age (yrs)		50-59	60-69	70+	Total
N		74	105	152	331
Basis for diagnosis					
Histology		97%	94%	94%	95%
Cytology		3%	6%	6%	5%
Stage					
I		28%	36%	26%	30%
II		24%	17%	17%	18%
III		11%	15%	18%	16%
IV		24%	25%	22%	24%
Unknown		12%	7%	16%	12%
Malignancy grade					
Low		27%	15%	10%	15%
Intermediate		57%	60%	59%	59%
High		1%	3%	5%	4%
Not Classified		15%	22%	26%	22%
Treatment Stage I	N	21	38	40	99
No treatment		-	-	13%	5%
Surgery (S)		14%	24%	22%	21%
Radiotherapy (RT)		5%	13%	35%	20%
Chemotherapy (CT)		19%	29%	12%	20%
S+RT		9%	16%	2%	9%
S+CT		14%	8%	7%	9%
RT+CT		24%	8%	5%	10%
Other		15%	2%	4%	6%
Treatment Stage II-IV	N	44	60	87	191
No treatment		4%	7%	16%	10%
Chemotherapy (CT)		77%	75%	57%	67%
CT+RT		4%	5%	8%	6%
Other		15%	13%	19%	17%
Treatment Stage Unknown	N	9	7	25	41
No treatment		-	14%	28%	19%
Treatment		22%	29%	36%	32%
Treatment unknown		78%	57%	36%	49%

The vast majority (94%) of patients with metastatic breast cancer received treatment, which usually comprised endocrine therapy (44%) or a combination of surgery and endocrine therapy (20%); however, more of the elderly women only received endocrine therapy than the younger ones. Nearly all of the patients with metastatic head and neck cancer were treated (91%). They received surgery and radiotherapy (43%) or only radiotherapy (30%); this also applied to the elderly patients. Furthermore, it was found that in the patients with a metastatic colorectal tumour, more of the women aged 70+ years did not receive treatment than the men within this age category, 40% and 21%, respectively. Otherwise no sex differences were found.

The elderly patients with a non-Hodgkin lymphoma stage I received radiotherapy (35%), surgery (22%) or chemotherapy (12%), while the younger patients received more often a combination of these treatments (see Table 4).
The majority of patients with a non-Hodgkin lymphoma stage 2, 3 or 4 received chemotherapy, but the percentage decreased with increasing age. In the three age categories 50-59 years, 60-69 years and 70+, the percentages were 77%, 75% and 57%, respectively (P=0.023). When the malignancy grade was also included in the analysis (data not shown), we found that only 10% of the patients with low grade disease, stage 1 (n=11), received radiotherapy alone, whereas this percentage was 45% in the patients with intermediate or high grade disease. In the patients with low grade disease, stage 2, 3 or 4, 50% received chemotherapy and 18% were not treated, whereas 74% of the patients with intermediate or high grade disease, stage 2, 3 or 4 received chemotherapy and 7% were not treated. The majority of patients who were not treated were 70 years of age or older.

Table 5 Odds ratios and 95% confidence intervals for no treatment according to age, adjusted for stage and sex; various sites, age: 50 years and older; IKL, 1988-1992

Site	Age (yrs)	Treatment no	Treatment yes	Odds Ratio	95% CI [a]
Head-Neck	50-59	5	106		1(ref) [b]
	60-69	7	156	1.0	(0.3-3.4)
	70+	13	125	2.7	(0.9-7.9)
Lung, small cell	50-59	9	117		1(ref) [b]
	60-69	29	174	2.2	(0.9-4.8)
	70+	49	114	5.5	(2.6-11.9)
Lung, non-small cell	50-59	70	232		1(ref) [b]
	60-69	206	482	1.4	(1.0-2.0)
	70+	418	441	3.2	(2.2-4.5)
Ovary	50-59	2	52		1(ref)[b]
	60-69	13	77	3.7	(0.8-17.5)
	70+	23	88	4.7	(1.1-21.4)
Non-Hodgkin lymphoma	50-59	2	72		1(ref) [b]
	60-69	5	100	1.8	(0.3-9.5)
	70+	26	126	7.4	(1.7-32.2)

[a] 95% confidence interval
[b] Reference category

The logistic regression analyses showed that, corrected for stage and sex, the chance of not receiving treatment increased with increasing age (see Table 5). In the colorectal cancer group, the effect of higher age depended on the tumour stage and the sex of the patient (see Table 6). The effect of age on the chance of not being treated was greater for women of 70 years and older than for men. Owing to the fact that nearly all of the breast cancer patients were treated, we investigated the effect of age on the chance of receiving one treatment modality versus a combination of two or more modalities. The results showed that a higher age at diagnosis increased the chance of only receiving one type of treatment (see Table 7).

Table 6 Odds ratios and 95% confidence intervals for no treatment according to age; patients with colorectal cancer aged 50 years and older; IKL 1988-1992

		Colorectal			
	Sex	Treatment		Odds ratio	95% CI[b]
		No	Yes		
Age (yrs)					
50-59		13	280		1(ref)[c]
60-69[a]		59	561	1.6	(0.8-3.3)
Age+Stage[d]	Men	2	346	0.8	(0.3-2.5)
70+ *Stage I-III	Women	7	399	1.4	(0.5-4.1)
70+ *Stage IV	Men	19	71	2.8	(1.2-6.3)
	Women	35	53	4.8	(1.7-10.7)
70+ *Stage Unknown	Men	30	23	2.7	(1.0-7.0)
	Women	37	20	4.6	(1.7-12.6)

[a] Adjusted for stage and sex
[b] 95% confidence interval
[c] Reference category
[d] The effect of age 70+ was different for men and women and depended on stage; therefore, the odds ratios are presented separately

Table 7 Odds ratios and 95% confidence intervals for one treatment modality versus two or more treatment modalities according to age; breast cancer, age 50 years and older; IKL, 1988-1992

Site	Age (yrs)	Treatment		Odds ratio	95% CI
		One	> One		
Breast	50-59	101	387		1(ref)[a]
	60-69	133	419	1.3	(0.9-1.6)
	70+	277	320	3.4	(2.6-4.5)

[a] Reference category

Discussion

Age-specific differences in the diagnostics and treatment of patients with various forms of cancer, diagnosed in the period 1988-1992, were investigated. Data on incident cancer cases and data on diagnostic procedures and treatment were obtained from the population-based Regional Cancer Registry Limburg.
Several findings indicated that elderly patients had undergone a less extensive diagnostic work-up: a larger proportion of unknown tumour stage among the elderly, a higher proportion of patients without a histologically or cytologically confirmed diagnosis, and a higher proportion of patients in whom the stage was based on less accurate diagnostic procedures (certainty factor). Furthermore, it could be concluded that a higher age increased the chance of not being treated or of receiving less intensive treatment.

The extent of the diagnostic work-up was derived from the basis for diagnosis and from the degree of certainty about the TNM classification (certainty factor). Our classification according to the certainty factor was rather rigorous and may have caused some misclassification. For example, a lung tumour which had a C0 for M, but C2 for T and C2 for N, which can be enough information to make the decision not to operate, was valued in this study as being insufficient diagnostic work-up. Also a rather high proportion of the certainty factor was missing for one or more parts of the TNM. Nevertheless, an association was found between the diagnostic work-up according to the certainty factor and age, suggesting a less extensive work-up at higher age.

The degree to which diagnostics and treatments differed and the nature of these differences depended on the localisation of the tumour. For head and neck cancer, for example, there were hardly any age-specific differences in the treatment modalities applied. It is possible that the heterogeneity within this group of tumours obscured any differences.
Lung cancer on the contrary, revealed large age-specific differences in the diagnostic work-up and treatment methods. This was probably related with the fact that lung cancer still has a very poor prognosis. For example with non-metastatic non-small cell lung cancer, older age decreased the likelihood of receiving surgery: 61% of the patients in the age category 50-59 years were operated on, while this was 50% in the 60-69 year olds and only 30% in those of 70^{+}years. A reluctancy to operate on elderly patients was described earlier by Smith et al. [21] for locoregional NSCLC. They studied differences in treatment patterns of lung cancer with data from incident cases from the Virginia Cancer Registry, 1985-1989. In their study comorbidity did not appear to have influence. However, over the past few years, various authors have argued in favour of considering tumour resection in elderly patients with a non-small cell lung carcinoma [15,22].

For breast and ovarian cancer, the total of stage 4 and stage unknown is much higher in elderly patients, which may indicate patient delay. A high percentage of elderly patients with advanced stage disease is in agreement with some studies [6,23,24] but not with other [25,26]. Especially for breast cancer the literature on the age-stage relationship is inconsistent [27].
Since the end of the 1980s, it was recommended not to treat elderly breast cancer patients with endocrine therapy alone (usually Tamoxifen) [28-30]. This policy was also recommended in our region and we found that a considerable proportion of the elderly patients received a combination of surgery and endocrine therapy: 27% for stage 1-3 patients and 12% for stage 4 patients. However, 14% of the elderly patients with breast cancer stage 1-3 and 59% of the elderly patients with advanced stage disease received endocrine therapy alone.

In the elderly patients with a metastatic colorectal tumour (n=178), more elderly women than elderly men did not receive treatment, 40% and 21% respectively, which is in agreement of earlier findings [8]. However, within this wide age category the average age of the women was higher than that of the men. Probably there was also more comorbid disease among the elderly women.

One of the factors that is of great importance for the prognosis of a patient with a non-Hodgkin lymphoma is the malignancy grade. In this study we found that 22% of the NHL patients could not be classified. Partly this was due to the fact that the diagnosis was based upon cytology only. Also, there is no classification according to the Working Formulation for a group of lymphomas which comprise 5% of the total of lymphomas (e.g. T-cell lymphoma). However, these two phenomena do not completely explain the high proportion of unclassified lymphomas, which may be partially due to a registration artefact. Furthermore, we had to be cautious with our analyses on this patient group, because stratifying the patients according to stage, malignancy grade and age sometimes produced very small numbers and consequently, dubious conclusions.
One of the advantages of using population-based data from a cancer registry is that bias on the basis of referral policies is excluded. If for example, patients are recruited for a study via a hospital registry, there is a risk that this will be a selected group. However, a cancer registry does not have at its disposal data on e.g. the dose of cytotoxic drugs administered, the number of treatment cycles, possible complications during treatment and whether the treatment was stopped prematurely. These are all factors that may be subject to age-specific differences that were not addressed in this study.

Also we did not have any information about comorbidity in our population of cancer patients, or about their functional and cognitive status, social circumstances and education level. These factors may have helped to explain why a patient had a less intensive diagnostic work-up or a less intensive treatment. Advanced stage disease with the associated series of diagnostic tests may be considered to be too much of a burden by a patient with poor physical or mental health, or by the family or the treating physician. In addition, if the treating physician feels defeatism or has misgivings about the efficacy of the treatment, this may lead to a less intensive policy. In the literature available on this subject, there is no consensus about the role that these factors play in the choice of treatment. In some studies, the age effect on the choice of treatment remained intact after correction for comorbidity [4,8], while in others the effect disappeared [14]. Within the group of elderly patients in the USA, associations have been found between no treatment and civil status, socio-economic status, transport facilities and the distance between home and the treatment centre [8,30].
In this study we confirmed the existence of age-specific differences in the diagnostics and treatment of cancer patients. However, we are just as much in the dark about the decision-making process about diagnostics and therapy in the elderly, as we are about the consequences of the age-specific differences observed, e.g. consequences for the patient in terms of survival and quality of life. In a group of breast cancer patients, Bergman et al. [6] found a difference in treatment between the younger and elderly patients, but not in survival. Gloeckler Ries [7] on the contrary concluded that for ovarian cancer, there were differences between treatment and survival: the younger patients had relatively higher survival chances than the older patients.

If the decision not to treat a patient is based on disease progression and on misgivings about treatment efficacy [14], then why is it that so many younger patients with more advanced stage cancer do receive treatment, while the older ones do not? Maybe we are under-treating the older patients, or over-treating the younger ones? More research is necessary to provide answers to these questions.

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3

Age-specific differences in treatment and survival of ovarian cancer patients in the province of Limburg, the Netherlands

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Abstract

The objective of this study was to investigate age-specific differences in treatment and survival of patients with epithelial ovarian cancer diagnosed in the period 1986-92 in Middle and Southern Limburg, the Netherlands.

Data about the treatment of epithelial ovarian cancer patients were derived from the population-based Maastricht Cancer Registry and retrospectively evaluated. Observed and relative survival rates were calculated according to age, stage, period of incidence and histology. Differences in survival between three age groups were explored with univariate and multivariate analyses. The patients were followed until 1 January, 1994.

The total study group comprised 367 epithelial ovarian cancer patients; 86 were younger than 55 years at diagnosis, 152 were 55-69 years and 129 were aged 70 years or older. Stage III (FIGO) was the most common stage at diagnosis in the three age groups. Older women (70^+) were more likely to have received no treatment or only one treatment modality than were younger women ($P<0.001$). Five-year relative survival decreased with age: 54%, 34%, and 17% in the three age groups 0-54, 55-69 and 70^+ years, respectively ($P=0.000$). Multivariate regression analysis revealed that age at diagnosis was an independent significant prognostic factor.

Several exposure factors in elderly women may explain the differences in treatment and survival, such as additional comorbid conditions, more aggressive tumour growth, physicians' reluctance to treat elderly patients and less favorable social conditions.

Introduction

Ovarian cancer is the fifth most common form of cancer among women in the province of Limburg, with an annual incidence rate of 13.4 per 100,000 women [1]. Of all gynecological malignancies, ovarian cancer is the most lethal; in the province of Limburg, nearly 63% of gynecological cancer mortality is due to ovarian cancer [1]. The incidence of ovarian cancer increases with age; the highest rates are found between the ages of 65 and 80 years.

Over the last 20 years, the prognosis of ovarian cancer has improved due to a combination of factors such as new treatment methods and improved supportive therapy [2,3]. However, the majority of women with the most common type of ovarian malignancy, epithelial cancer, have advanced disease (stages III and IV) at diagnosis [4,5].

Several authors [4,6-8], also in the Netherlands [9] have described that older ovarian cancer patients do not receive the same treatment as younger patients. Elderly women were more likely not to have been treated than were younger patients and had more frequently received only one treatment modality (surgery or chemotherapy). Age-specific survival was examined in several studies [6-8,10-13], but the patients were recruited from hospital registries [6,7,12] or data were derived from trials [8,10,11,13] which may have led to selected patient groups. In contrast, Högberg et al. [14], Levi et al. [15] and Gloeckler Ries [3] analysed ovarian cancer data collected by national or regional population-based cancer registries in Sweden, Switzerland and the United States, respectively. Besides the examination of treatment patterns, they calculated survival rates and, to account for noncancer mortality which is higher in the elderly, they computed relative survival rates. They found that younger patients had higher survival rates than older ovarian cancer patients. Recently, trends in ovarian cancer incidence and mortality have been studied in the Netherlands [16], but no comprehensive studies on the diagnostics, treatment and survival of patients with ovarian cancer have been performed. Different approaches were employed by van Houwelingen et al. [17] who constructed a prognostic index for long-term survival of ovarian cancer patients treated with chemotherapy and by Balvert-Locht et al. [2] who examined the improvement in the prognosis of ovarian cancer in the Netherlands over the period 1975-1985.

To obtain further information on the management and survival of ovarian cancer patients we conducted a population-based study in the province of Limburg, the Netherlands, with special attention to the impact of age.

Patients and methods

Data collection

Data on incident ovarian cancer cases and their treatment were obtained from the Maastricht Cancer Registry, a department of the Comprehensive Cancer Centre Limburg (IKL). This population-based cancer registry covers the regions of Middle and South Limburg, with about 850,000 inhabitants, comprising approximately 5.6% of the Dutch population (for a description of the region and registration procedures see Schouten et al [18]).

Information on the survival of all ovarian cancer patients included in this study was collected by means of active follow-up. The vital status of the patients has been verified up to 1 January, 1994.

Study population

Between January 1, 1986 and December 31, 1992, 452 women were diagnosed with cancer of the ovary within the IKL catchment area. We excluded any patients who had a previous malignancy (n=35), whose diagnosis had not been made until autopsy (n=2) or whose ovarian tumor was of borderline malignancy (n=2); 413 patients were studied. Because germ cell and sex cord tumors chiefly affect young women and have different (more favourable) survival rates than epithelial tumors of the ovary, only patients with an epithelial tumor were included in the analyses (n=367). Serous, mucinous, endometrioid and clear cell tumours, as well as adenocarcinoma not otherwise specified (NOS), were considered epithelial tumors.
Despite active follow-up, 10 cases (2.7%) had to be excluded from the survival analysis, because no date of last contact or date of death could be traced.

Variables

Variables included age (categories: 0-54, 55-69, 70^{+} years); FIGO (International Federation of Obstetrics and Gynaecology) stage [19]; histology; period of diagnosis; treatment and survival data. Tumour stage referred to the extent of the disease at the time that the definitive decision about the treatment policy was made. Based on comparable treatment modalities, cases were grouped together for some analyses: stages I+II and stages III+IV. Time of diagnosis was divided into two categories by calendar year: 1986 through 1989 and 1990 through 1992. This choice was made, not because of a change in treatment options, but because of small numbers. Treatment referred to the primary treatment received by the patients in the first three months after diagnosis.

Data analysis

We analyzed the relationships between age and treatment using the Pearson chi-square test and the Mantel-Haenszel chi-square test for trend. Survival time was calculated from the date of diagnosis to the date of last contact or death. Observed survival rates were calculated according to the actuarial method (life-table) [20]. Mortality from competing causes may bias survival patterns, especially in the elderly. Reliable information about the actual cause of death was difficult to obtain, which is why relative survival rates were computed, using the methods and software developed by Hakulinen *et al.* [21]. Relative survival can be defined as the probability that a cancer patient will survive for a defined short period, divided by the probability that an age- and gender-matched individual will survive for the same period [22]. In addition, length of life expectancy was calculated using mean death rates and expected lifetimes for the female population in the province of Limburg 1986-1992. Death rates were provided by Statistics Netherlands (CBS).

Differences in relative survival rates between the various age and stage groups were tested using maximum likelihood ratio tests [23]. Observed survival rates were tested for equality with the logrank test. To estimate the independent effects of age, stage, histology, period of diagnosis and treatment, we performed multivariate regression analyses, using PROC GENMOD in SAS for relative survival rates and PROC PHREG in SAS for observed survival rates (Cox model). In PROC GENMOD, using relative rates, we calculated multiplicative risk ratios using a Poisson distribution [24].
Patients were sometimes registered as being alive on a certain date, but additional information on their status at the closing date of the study (1/1/1994) could not be found. Therefore these cases (N=18) were censored from the analysis from the last date of contact (12 were 70 years or older and 9 had stage III or IV tumors).

Results

We studied 367 patients with epithelial ovarian cancer, ranging in age from 16 to 89 years, (mean 63; median 65.5). Histological distribution is shown in Table 1. About 38% of the histologically specified adenocarcinomas were serous carcinomas. Mucinous tumors were less frequent (11%) as were endometrioid (7%) and clear cell carcinomas (5%). A fairly large proportion of the tumors (36%), however, were registered as adenocarcinomas without any further specification; this occurred most frequently in the 70+ age group. Furthermore, the majority (82%) of these unspecified adenocarcinomas were stage III or IV.
Table 1 also shows the stage distribution by age. FIGO stage III was the most common stage at diagnosis in the three age groups: 45%, 47% and 46% respectively. Within the stage categories I+II, the proportion of patients with stage I decreased significantly with age (*P-trend*= 0.034), while within the stage categories III+IV, the proportion of patients with stage IV increased slightly with age (*P-trend*= 0.425).

Table 1 Epithelial ovarian tumours: distribution according to age group, FIGO stage and histological type (%); Maastricht Cancer Registry, 1986-1992

	Age (yrs)			
	0-54	55-69	70+	Total
N	86 (100)	152(100)	129(100)	367(100)
FIGO stage				
I	27 (32)	31 (20)	18 (14)	76 (21)
II	6 (7)	17 (11)	13 (10)	36 (10)
III	39 (45)	71 (47)	59 (46)	169 (46)
IV	13 (15)	29 (19)	27 (21)	69 (19)
Unknown	1 (1)	4 (3)	12 (9)	17 (5)
Histological type				
Adenocarcinoma NOS[a]	29 (34)	50 (33)	55 (43)	134 (36)
Clear cell	4 (5)	10 (7)	3 (2)	17 (5)
Endometrioid	6 (7)	9 (6)	9 (7)	24 (7)
Serous	31 (36)	68 (45)	41 (32)	140 (38)
Mucinous	15 (17)	14 (9)	13 (10)	42 (11)
Unspecified	1 (1)	1 (1)	8 (6)	10 (3)

[a] NOS: not otherwise specified

Treatment

Treatment of stages I-II

Standard treatment for ovarian cancer stages I-II was surgery or surgery followed by chemotherapy [25]. This group comprised 112 patients, two of whom (1.8%) were not treated (both stage II, age at diagnosis 77 and 79 years, respectively). Large proportions of both the youngest (51%) and the oldest age groups (48%) were treated with surgery only, whereas 60% of the patients aged 55-69 years received surgery followed by chemotherapy.

Treatment of stages III-IV

Standard treatment for ovarian cancer stages III-IV was surgery followed by chemotherapy [25]. This group comprised 238 patients, of whom 32 (13.5%) were not treated. Per age category 0-54, 55-69 and 70+ years, these percentages were 2%, 13% and 21%, respectively (treated *vs* not treated: *P*-trend=0.002). Furthermore, the proportion of patients treated with chemotherapy alone increased with age: 22%, 28% and 37%, respectively (chemotherapy *vs* other therapy: *P*-trend=0.06), while the proportion of patients who received surgery followed by chemotherapy decreased with age: 71%, 54% and 37%, respectively (surgery+chemotherapy *vs* other therapy: *P*-trend=0.001).

Treatment of stage unknown

The stage of disease was unknown in 5% (n=17) of the patients; the majority (n=12) were 70 years or older. About 29% of these patients were not treated, the majority of whom were 70 years or older.

Table 2 Distribution of treatment according to age and stage in epithelial ovarian cancer patients (%); Maastricht Cancer Registry, 1986-1992

	Age 0-54 yrs			Age 55-69 yrs			Age 70+ yrs			Total
	Stage			Stage			Stage			Stage
Treatment	I-II	III-IV	X*	I-II	III-IV	X	I-II	III-IV	X	All
No treatment	-	1 (2)	-	-	13 (13)	-	2 (6)	18 (21)	5 (42)	39 (11)
Surgery (S)	17 (51)	3 (6)	1(100)	17 (35)	5 (5)	-	15 (48)	3 (4)	-	61 (16)
Chemotherapy (CT)	1 (3)	11 (22)	-	1 (2)	28 (28)	1 (25)	3 (10)	32 (37)	3 (25)	80 (22)
S + CT	15 (45)	36 (70)	-	29 (60)	54 (54)	3 (75)	11 (35)	32 (37)	2 (17)	182 (50)
Other	-	1 (2)	-	1 (2)	-	-	-	1 (1)	2 (17)	5 (1)
Total	33(100)	52(100)	1(100)	48(100)	100(100)	4(100)	31(100)	86(100)	12(100)	367(100)

*X= unknown

Treatment according to period of incidence
We did not find any differences in the treatment distribution over the two periods of diagnosis, 1986-89 and 1990-92 (Table 2).

Survival

Overall observed survival was 68% after one year, 40% after 3 years and 29% after 5 years. Overall relative survival rates were 70% after one year, 45% after 3 years and 36% after 5 years. Differences between relative and observed survival rates were most apparent in the oldest age group, which was to be expected (see Table 3). Survival rates varied with histology, stage and age. Patients with serous carcinoma had a poorer prognosis than those with clear cell, mucinous or endometrioid carcinoma, with 5-year relative survival rates of 37%, 56%, 59% and 65%, respectively. When nonspecified adenocarcinoma was compared to specified adenocarcinoma (serous, mucinous, endometrioid, clear cell carcinomas), we found that the 5-year relative survival was 22% in the nonspecified group *vs* 45% in the specified group (P=0.001).
In patients with FIGO stages I, II, III and IV tumors, 5-year relative survival rates were 90%, 32%, 24% and 9%, respectively, (P=0.001). Survival rates varied greatly with age (Table 3). Age differences in relative rates remained valid even after the analysis was stratified for stages I-II (P=0.056) and stages III-IV (P=0.0001).
No differences in survival rates were observed between the two periods of diagnosis, 1986-89 and 1990-92.

Loss in life expectancy

Mean life expectancy in a normal population matched for age and sex was 16.2 years compared to only 6.7 years (95% CI: 5.5-7.8) in our patients. This corresponded with a loss in life expectancy of almost 59%. Loss in life expectancy was 35%, 48%, 71% and 85% in women with stages I, II, III and IV ovarian cancer, respectively. In the general population, women in the 70+ age group who were living in the IKL catchment area between 1986 and 1992 could expect to live for a further 7 years on average. In the 70 years and older patient group, in contrast, life expectancy was approximately 2.5 years (95% CI: 1.6-3.3), a decrease of almost 66%. In the youngest group this decrease was almost 45% and in the 55-69 year group about 59%.

Table 3 Observed and relative survival rates of women with epithelial ovarian cancer by age, stage and histology; Maastricht Cancer Registry, 1986-1992

		Observed survival				Relative survival			
	N	1 year	3 year	5 year	P-value[a]	1 year	3 year	5 year	P-value[b]
Overall	357	68%	40%	29%		70%	45%	36%	
Age groups									
0-54 yrs	85	86%	60%	53%	0.0001	86%	61%	54%	0.0001
55-69 yrs	151	73%	42%	29%		74%	45%	34%	
70+ yrs	121	48%	21%	10%		52%	28%	17%	
Stage I-II									
all	111	89%	76%	62%		91%	83%	73%	
0-54 yrs	33	97%	94%	85%	0.001	97%	95%	86%	0.056
55-69 yrs	48	92%	76%	58%		93%	81%	66%	
70+ yrs	30	76%	56%	34%		81%	70%	51%	
Stage III-IV									
all	230	59%	24%	16%		61%	28%	20%	
0-54 yrs	51	78%	40%	33%	0.0001	79%	40%	33%	0.0001
55-69 yrs	99	69%	29%	18%		66%	31%	20%	
70+ yrs	80	39%	8%	3%		43%	12%	5%	
Histology									
Adenocarc. NOS[c]	140	60%	26%	17%	0.0-001[e]	63%	31%	22%	0.0001
Adenocarc. specified[d]	217	73%	48%	38%		75%	53%	45%	
Clear cell	16	69%	61%	50%		70%	65%	56%	
Endometrioid	24	75%	64%	53%		78%	73%	65%	
Serous	137	72%	42%	31%		74%	47%	37%	
Mucinous	40	75%	56%	50%		77%	61%	59%	

[a] Logrank test
[b] Maximum Likelihood Ratio test
[c] NOS: not otherwise specified
[d] Specified adenocarcinomas together: clear cell+ serous+ mucinous+ endometrioid carcinoma
[e] Adenocarcinoma NOS *versus* adenocarcinoma specified

Multivariate analyses

Multivariate regression analyses were performed using the relative survival rates as well as the observed rates. Variables were age (categorical), FIGO stage (stages II-II, reference category; stages III-IV; stage unknown), histology (adenocarcinoma specified *vs* adenocarcinoma NOS), treatment (surgery + chemotherapy yes/no) and period of diagnosis. In the model that used relative rates, duration of follow-up was defined by a categorical variable with 8 levels, each of 1 year. However, the 6th, 7th and 8th years of follow-up were grouped together because of small numbers. When testing for the significance of individual variables, age, stage and treatment were independent prognostic factors; histology and period of diagnosis did not approach statistical significance and were therefore not included in the models.
Risk ratios increased with increasing age with the model that used observed survival rates as well as with the model that used relative rates (see Table 4). In addition, advanced stage (III+IV) was associated with an increased risk of dying. Women who had been treated with a combination of surgery and chemotherapy had better survival rates. When the models were applied to the selected group of patients treated with this 'optimal' combination of treatment modalities, (n=182, of whom 181 were evaluable for survival analysis), we found that even within this group, age and stage were independent prognostic factors (see Table 5).

Table 4 Relative risks (RR) of dying and 95% confidence intervals (CI) estimated with observed and relative survival rates, according to age, stage and treatment in epithelial ovarian cancer patients; Maastricht Cancer Registry, 1986-1992

		Model with observed survival rates			Model with relative survival rates		
Variables	N	RR	95% CI	P-value	RR	95% CI	P-value
Age groups							
0-54 yrs	85	1(ref)[a]			1(ref)[a]		
55-69 yrs	151	1.59	1.07-2.37	0.0224	1.59	1.07-2.37	0.0001
70+ yrs	121	2.49	1.66-3.74	0.0001	2.72	1.81-2.39	0.0209
FIGO stage							
I+II	111	1(ref)[a]			1(ref)[a]		
III+IV	230	3.61	2.41-5.39	0.0001	3.63	2.46-5.35	0.0001
Unknown	16	2.83	1.41-5.68	0.0035	2.79	1.42-5.48	0.0030
Treatment							
Surgery + Chemotherapy	181	0.68	0.51-0.90	0.0068	0.66	0.50-0.87	0.0035

[a] reference category

Table 5 Relative risks (RR) of dying and 95% confidence intervals (CI) estimated with observed and relative survival rates, according to age and stage in epithelial ovarian cancer patients treated with surgery and chemotherapy; Maastricht Cancer Registry, 1986-1992

		Model with observed survival rates			Model with relative survival rates		
Variables	N	RR	95% CI	P-value	RR	95% CI	P-value
Age groups							
0-54 yrs	51	1(ref)*			1(ref)*		
55-69 yrs	85	1.94	1.14-3.30	0.0143	1.96	0.14-1.20	0.0131
70+ yrs	45	2.72	1.53-4.83	0.0006	2.89	1.63-5.13	0.0003
FIGO stage							
I+II	53	1(ref)*			1(ref)*		
III+IV	121	2.54	1.50-4.31	0.0005	2.47	1.46-4.20	0.0008
Unknown	5	1.61	0.47-5.57	0.4515	1.53	0.82-5.28	0.5030

* reference category

Discussion

The present study investigated age-specific differences in the management and survival of 367 women diagnosed with epithelial ovarian cancer. We found that women aged 70 years and older were more likely to have received no treatment or only one treatment modality than younger women. In contrast, the majority of younger patients were treated with both surgery and chemotherapy. Survival analyses showed that the overall prognosis for epithelial ovarian cancer was poor and even more unfavorable in the elderly patients. Overall 5-year relative survival was 36%, which was in agreement with Balvert-Locht [2] and Högberg [14] who reported overall 5-year relative survival rates of 32% and 40%, respectively. In the present study, 5-year relative survival rates in the three age groups were 54%, 34% and 17%, respectively. Calculating relative survival rates takes into account mortality from noncancer-related disorders, which not only explains the differences between the observed and relative rates (increasing with age), but also the smaller differences in the relative rates compared to the observed rates between the three age groups.

The survival of women with serous adenocarcinoma was considerably shorter than that of women with other specified adenocarcinoma. Two other population-based studies, one in Iceland [26] and one in Switzerland [15], compared survival rates of epithelial ovarian cancer of different histological types. In Iceland, women with endometrioid carcinoma had five-year survival rates that were similar to those with serous carcinoma, whereas in Switzerland women with endometrioid carcinoma had a significantly better prognoses than those with serous cancer, which was in agreement with our findings.
We found that 36% of all epithelial ovarian tumors had no further specification than adenocarcinoma. In a SEER publication [27], the incidence of adenocarcinoma NOS and papillary adenocarcinoma NOS were, in contrast to our study, reported separately, and these two categories together accounted for almost 30%, which is comparable to our finding.

However, series with lower proportions of adenocarcinoma NOS were also reported. Levi *et al.* [15] reported that 22% of epithelial ovarian cancers had not been histotyped, while in a recent review article in Lancet [28] Kristensen mentioned only 10% unclassified histotypes, cited from the 1995 Swedish annual report. In contrast with Levi *et al.*, the percentage of epithelial ovarian cancers in our population that had not been histotyped was higher in the oldest age group.

Although this population-based study had the advantage of an unselected patient group, the registry did not record data on other important prognostic factors, such as the presence or absence of residual disease after surgery, malignancy grade and the presence or absence of ascites. In addition, other unrecorded treatment aspects, such as dosage reduction, premature ending of treatment and complications during or after treatment may be age-related.
Several possible explanations have been put forward to explain the differences in survival between younger and older women with ovarian cancer. First, the unfavorable survival of elderly patients could be the consequence of more comorbidity among the elderly, which results in higher (noncancer-related) mortality in this group [6]. Calculating relative survival rates takes this noncancer mortality into account, but the presence of another illness may have a major influence on whether a complicated operation should be performed or burdensome chemotherapy should be administered. Studies in which comorbidity was taken into account are scarce, but results from trials have shown that the performance status of patients was an important prognostic factor [10,11,13].
Second, it has been suggested that ovarian cancer may be a more aggressive disease in the elderly, with earlier development of drug resistance, tumour spread or involvement of vital organs [2,6]. Currently, there is no direct evidence to support this conclusion.
Third, it has been claimed that elderly women tend to present with more advanced stage ovarian cancer than younger women [3,29] which was confirmed in our data. Gloeckler Ries even suggested that older women may have more advanced disease even within stages III and IV [3]. Surgery (laparotomy), besides being the initial therapy for ovarian cancer, is the cornerstone of adequate staging. Staging laparotomy is an extensive and fairly complicated operation that needs a thorough understanding of the pathogenesis of the disease. Although staging procedures improved the last two decades [2], some reluctance towards the reliability of the defined stages may still be appropriate.
Fourth, employing less aggressive or less intensive treatment policies for elderly women has been put forward as an explanation for survival differences. According to several authors [7,8,12] older women were more likely to start chemotherapy with bulky disease than younger women. However, Marchetti *et al.* [12] found that the difference in survival remained valid even within a group of patients who had all received optimum therapy. In our study, age-specific differences remained valid within the group of patients who had undergone surgery and chemotherapy. However, detailed information about the meticulousness of the operation and the type of chemotherapy was not available.

In summary, differences in treatment cannot fully account for the differences in survival between younger and older women with ovarian cancer. The most plausible explanation is that older women are more likely to have exposure to factors that negatively influence cancer survival, such as a poor physical condition, aggressive tumour growth, reluctance of doctors to apply standard cancer treatment to older patients and a less favorable social situation.

In general, physicians agree that all cancer patients must be treated equally, regardless of age. Theoretically this may be correct, but in practice physicians can hardly ignore the age of a patient, as age is strongly related with other factors that affect treatment choice. Perhaps the age of the patient should be the starting point for the discussion about how to treat that particular patient, while successively taking all other relevant factors into account.

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4

Age-specific differences in treatment and survival of patients with cervical cancer in the southeast of the Netherlands

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Abstract

Age at diagnosis has proven to be an important determinant of the choice of initia treatment for several sites of cancer. Elderly patients are more likely to receive n treatment or less intensive treatment modalities. This study analysed the influence of ag on treatment choice and survival in patients diagnosed with cervical cancer.

This population-based study used data on 1176 new cases of invasive cervical cance diagnosed in the period 1986-1996 from three regional cancer registries in th Netherlands. All available information on treatment and survival (on January 1st 1998 was recorded. Relative survival rates were calculated according to the Hakulinen method Relative risks for excess mortality due to the diagnosis of cervical cancer were calculate with a regression model for relative survival rates.

Only 5% of the patients aged 70 years and older (n=224) were diagnosed with stage I/ disease, compared to 11% and 30% of the patients aged 50-69 years and 49 years an younger, respectively. Almost 50% of the 70+ patients with stage IB-IIA were treate with radiotherapy as a single treatment modality, whereas 64% of the patients <= 4 years were treated with surgery. In all age groups, treatment for advanced stage diseas (stage > IIB) was radiotherapy alone. No treatment was applied to 10% of the patient aged 70 years and older, 5% of those aged 50-69 years and and 1% of those aged 49 years and younger. Five-year relative survival was 69% (95% Confidence Interval: 66%-72%) and differed significantly (p=0.001) with age (70+ years: 49%; 50-69 years 58%; <= 49 years: 81%). Multivariate analyses on a subset of patients showed that age was not an independent prognostic factor, whereas stage and treatment modality were very important prognostic factors.

Although elderly cancer patients were sometimes treated differently from younger patients, this was in accordance with the guidelines. Relative survival rates differed significantly by age. The multivariate analyses on the subset of patients also revealed that excess mortality increased with age. However when adjustment was made for stage and treatment, the increase disappeared. The influence of treatment on survival is likely to be due to the selection of patients based on other characteristics, such as tumour volume, comorbidity and performance status.

Introduction

The prognostic significance of age in cervical cancer has been the subject of several studies since the early 1970s. The approach to studying age at diagnosis as a prognostic factor has not always been the same. Frequently, the question of whether young patients have a poorer prognosis than older patients was the central point of interest [1-5]. The assumption was that cancer is biologically more aggressive in younger patients. Other studies [6,7] associated older age with a poorer prognosis, assuming that elderly patients receive less aggressive and hence, inappropriate treatment thus influencing their survival [8]. Several other survival studies on cervical cancer in general or evaluation studies on screening programmes [9-19] included age as a prognostic factor in the survival analysis. Nevertheless, it is still not clear whether age is an independent prognostic factor in cervical cancer. To date, very few population-based studies have been published. One of the advantages of using population-based data from a cancer registry is that bias from referral policies is excluded. Studies on differences in patterns of care between older and younger cervical cancer patients are fairly scarce and the emphasis has mostly been on survival. The present population-based study is embedded in a regional project on cancer in the elderly [20-22]. The purpose was twofold: firstly, to study differences in treatment patterns for cervical cancer in elderly patients compared to younger patients and secondly, to study age-specific relative survival.

Patients and methods

Data collection

The data for this study were obtained from three regional cancer registries: the Eindhoven Cancer Registry (eastern part) over the period 1986-1994, the Cancer Registry of the Comprehensive Cancer Centre East over the period 1989-1995 and the Maastricht Cancer Registry over the period 1986-1996. The total area represented a population of around 3 million in 1990. For a description of the regions and registration procedures, see Schouten et al [23], Parkin et al [24] and Van der Sanden et al [25].

Study population

Data on patients with newly diagnosed invasive cervical cancer registered at one of the three registries were analysed. Patients who had a previous malignancy other than basaloid skin cancer, or had been diagnosed at autopsy, or had tumours with a rare histology (leiomyosarcoma (n=10), endometrial stromal sarcoma (n=2)) or tumours without a pathological diagnosis (n=3), were excluded, leaving 1176 patients. Information on the vital status up to January 1st 1998 was collected by means of active follow-up.

Variables

Tumour stage was defined according to the 1989 FIGO staging system [26], preferably based on pre-treatment information. In 237 cases in whom pre-treatment stage information could not be extracted from the medical files, post-surgical information was used. Patients with pathological stage IIB-IVA (n=27) were assumed to have clinical stage IB-IIA, as surgery is not the standard treatment for IIB-IVA tumours. Therefore these patients were included in the analysis as IB-IIA cases [27]. Patients were categorised by stage, which resulted in five categories: IA, IB-IIA, IIB-IVA, IVB and unknown. These categories were chosen because treatment guidelines within these stages are uniform. During the study period, the treatment of first choice for stage IA and IB-IIA was surgery, especially in younger patients in order to preserve ovarian function, whereas radiotherapy was the treatment of first choice for locally advanced disease (i.e. stage IIB and higher) and in older patients and/or increased operation risk [27].
In this study treatment refers to the primary treatment modality applied during the first three months after diagnosis. It classified as surgery, radiotherapy, surgery+radiotherapy and other/none (other treatment modalities such as chemotherapy / no initial treatment). Treatment is described according to age and FIGO stage.

Analyses

Survival was defined as the period between diagnosis and death, irrespective of the cause of death. As reliable information on the actual cause of death was lacking, correction for death from competing causes was achieved by computing relative survival according to the Hakulinen method, using the Finnish Cancer Registry survival software [28]. Relative survival is defined as the probability that a cancer patient will survive over a defined short period, divided by the probability that an age-matched individual will survive over the same period [29]. The latter figures were calculated from life tables (supplied by Statistics Netherlands) compiled according to sex and year of diagnosis in the regional population. Comparisons between groups were made by means of a likelihood-ratio test. A multiple regression procedure [30] analogous to the Cox model [31] was used to evaluate the simultaneous effect of several prognostic factors on relative survival in a selected group of patients (treated with surgery, radiotherapy or a combination of the two for stage IB-IVA squamous cell carcinoma and adeno(squamous)carcinoma). Cases with stage IA and IVB were excluded from these multiple regression models. The former because of a low number of events (death) and the latter because treatment was palliative and strongly individualised. Cases with unspecified histology and cases who did not receive surgery, radiotherapy or both were also excluded, because of low numbers and in order to create a fairly homogeneous group of patients. Age, stage and treatment factors were introduced in the models, as well as duration of follow-up (five levels, each of one year duration) and histological type (squamous cell carcinoma, adeno+adenosquamous carcinoma).

Table 1 Patient characteristics

Age (yrs)	<=49		50-69		70+		Total	
	N	%	N	%	N	%	N	%
Total	612	100	340	100	224	100	1176	100
Stage (FIGO)								
IA	185	30	39	11	12	5	236	20
IB	278	45	98	29	51	23	427	36
IIA	46	8	54	16	34	15	134	11
IIB	50	8	48	14	42	19	140	12
IIIA	3	<1	6	2	9	4	18	2
IIIB	18	3	46	14	33	15	97	8
IVA	6	1	22	7	12	5	40	3
IVB	14	2	18	5	14	6	46	4
Unknown	12	2	9	3	17	8	38	3
Histology								
Squamous cell ca	454	74	267	79	169	75	890	76
Adenocarcinoma	108	18	54	16	44	18	206	17
Carcinoma NOS	50	8	19	6	11	5	80	7
Basis for Diagnosis								
Cytological	2	<1	3	1	10	4	15	1
Histological	610	100	337	99	214	96	1161	99

Results

Table 1 shows the characteristics of the entire patient population. The distribution of cases by age reflects the rather young age at which this type of gynecological cancer occurs. 52% of the cases were aged <= 49 years, 29% were 50 to 69 years and 19% were 70 years or older. More younger patients had early stage tumours, while more older patients had advanced stage disease. Histological types were equally distributed among the three age categories. The diagnosis had been histologically confirmed in more than 99% of the patients of younger than 70 years and in 95% of those aged 70+ years.

Treatment

Stage IA

Most of the stage IA cases had been treated surgically (87%). Above the age of 70 years, the number of cases with stage IA was small (n=12). These 70+ patients were treated with surgery (58%), radiotherapy (25%), or a combination of the two (8%). One of the elderly patients was not treated.

Stage IB-IIA

In the age groups 70+ years, 50-69 years and <= 49 years, radiotherapy had been the single treatment modality in 48%, 25% and 8% of the patients, respectively. For surgery, these proportions were 22%, 40% and 64%, respectively. Surgery followed by radiotherapy was received by 27%, 33% and 25% of the patients, respectively (Figure 1).

Stage IIB-IVA
Some of these patients did not receive curative treatment, especially in the 70+ age group (12.5%). This percentage was 6% in the 50-69 year age group, whereas all patients aged 49 years and younger received curative treatment. Most patients were treated with radiotherapy alone, i.e. 76% of the patients aged 70 years and older, 86% of the patients aged 50-69 years and 73% of the patients aged 49 years and younger.

Stage IVB
Treatment for women with stage IVB cervical cancer (n=46) was palliative and strictly individualised (surgery, RT, chemotherapy and combinations of these). A total of 14 patients had not been treated, of whom 3 patients were aged 49 years or younger, 7 were aged 50-69 years and 4 were aged 70+ years.

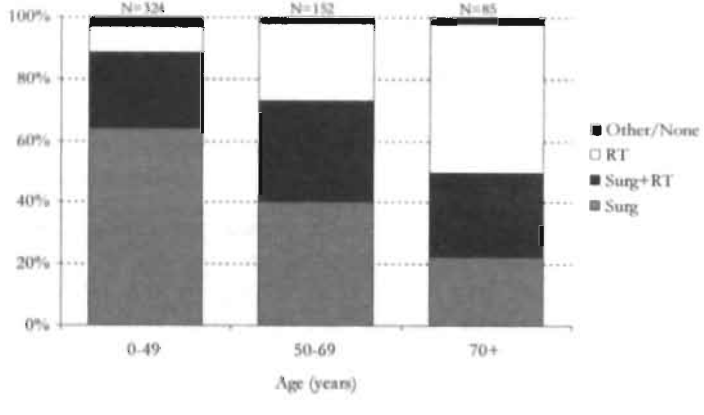

Figure 1 Initial treatment for patients with cervical cancer stage IB-IIA, 1986-1996; RT, radiotherapy; Surg, surgery

Survival

Overall relative 5 year survival was 69%. Cumulative relative survival rates at 1, 3 and 5 years after diagnosis, stratified by age and stage, are shown in table 2. Older patients had a poorer prognosis (LR test: p=0.000) (Table 2; Figure 2a-2b). The survival difference between the three age groups was most prominent in patients with stage IIB-IVA disease (LR test: p=0.008).
Table 3 shows 1, 3 and 5 year relative survival rates stratified by histological type and age. In the oldest age category, patients with squamous cell carcinoma had better 5 year survival than those with adenocarcinoma, i.e. 54% versus 37%, although this difference was not statistically significant (LR test: p=0.4).

Univariate and multivariate estimated relative risks of excess mortality are shown in Table 4. Relative risks for age 50-69 years and 70+ years, adjusted for stage and histology, were both significantly higher than the risks in the reference category <= 49 years. When treatment was included in the model, the relative risks for the three age groups were no longer significant.

Table 2 Number of cases (N) and cumulative relative survival at 1, 3 and 5 years after diagnosis; 95% confidence intervals for the 5-year rates, stratified by stage and age

			Relative survival (%)			
Stage	Age (yrs)	N at risk	1 year	3 year	5 year	5 year 95% CI*
IA	<=49	185	100	99	97	93-99
	50-69	39	100	96	95	80-100
	70+	12	99	85	88	45-100
	All	236	100	98	97	92-99
IB-IIA	<=49	324	95	85	81	76-86
	50-69	152	94	81	74	66-81
	70+	85	93	80	73	58-87
	All	561	95	83	78	74-82
IIB-IVA	<=49	77	79	55	50	39-62
	50-69	122	74	46	34	25-43
	70+	96	56	34	30	19-43
	All	295	70	45	37	31-44
IVB	<=49	14	29	20	20	7-48
	50-69	18	39	17	17	6-41
	70+	14	15	8	-	-
	All	46	29	14	14	7-29
Unknown	<=49	12	100	92	92	65-99
	50-69	9	78	57	46	19-76
	70+	17	71	68	59	29-96
	All	38	82	73	68	48-85
All stages	<=49	612	93	84	81	78-84
	50-69	340	84	66	58	52-64
	70+	224	71	55	49	41-59
	All	1176	87	74	69	66-72

*CI=Confidence interval

Table 3 Number of cases (N) and cumulative relative survival at 1, 3 and 5 years after diagnosis; 95% confidence intervals for the 5-year rates stratified by histological type and age

			Relative survival (%)			
Histology	Age (yrs)	N at risk	1 year	3 year	5 year	5 year 95% CI*
Squamous cell carcinoma	<=49	454	93	84	80	76-84
	50-69	267	86	67	58	52-65
	70+	169	72	60	54	44-65
	All	890	87	75	67	66-73
Adenocarcinoma	<=49	108	96	87	83	75-90
	50-69	55	86	64	56	42-69
	70+	44	68	39	37	20-60
	All	207	88	72	69	61-76
Carcinoma not otherwise specified	<=49	50	84	82	82	70-91
	50-69	19	64	59	60	38-80
	70+	11	66	31	23	6-61
	All	80	77	70	70	59-80

* CI=Confidence interval

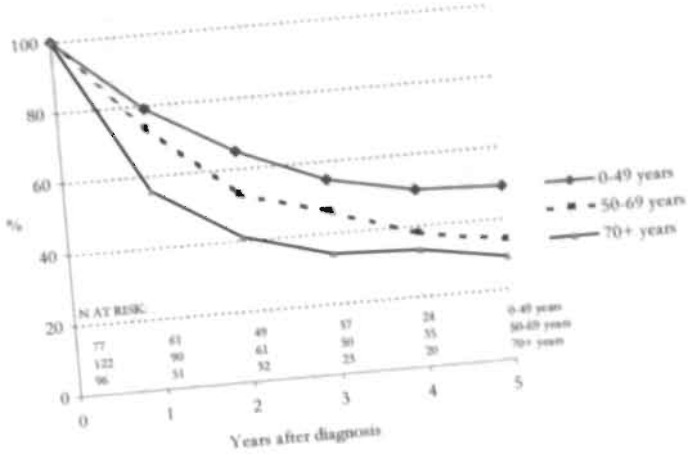

Figure 2a Relative survival rates by age, cervical cancer stage IB-IIA

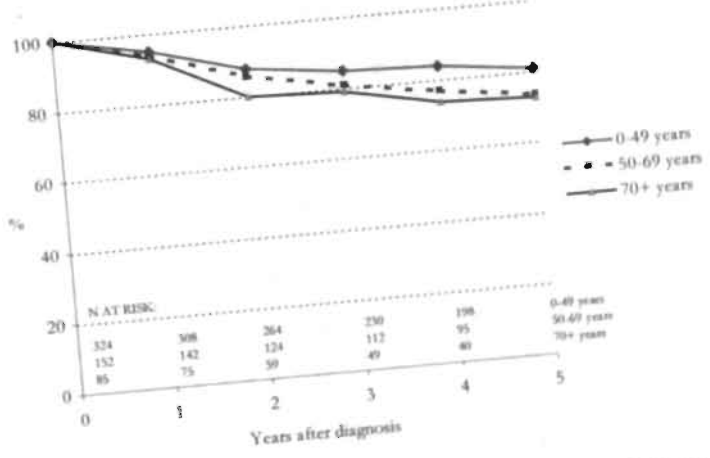

Figure 2b Relative surivival rates by age, cervical cancer stage IIB-IVA

Table 4 Results of univariate and multivariate analysis; estimated relative risks for excess mortality and associated 95% confidence intervals (N=783)[a]

	N	Univariate RR (95% CI)[b]	P-value[c]	Multivariate[d]	P-value	Multivar.+treatment[e] RR (95% CI)	P-value
Age							
< = 49 years	374	1 (reference)	0.00	1 (reference)	0.01	1 (reference)	0.42
50-69 years	254	2.1 (1.6-2.9)		1.5 (1.1-2.1)		1.2 (0.9-1.7)	
70+ years	155	2.5 (1.7-3.6)		1.7 (1.2-2.5)		1.2 (0.8-1.8)	
Stage							
IB-IIA	529	1 (reference)	0.00	1 (reference)	0.00	1 (reference)	0.00
IIB-IVA	254	4.5 (3.4-6.0)		3.7 (2.8-5.0)		2.1 (1.5-2.9)	
Histology							
squamous cell	639	1 (reference)	0.74	1 (reference)	0.09	1 (reference)	0.06
adenocarcinoma	144	1.1 (0.8-1.6)		1.3 (1.0-1.9)		1.4 (1.0-2.0)	

[a] Patients diagnosed with stage IA, IVB or stage unknown and patients who were not treated or in whom treatment was not known were excluded
[b] RR: Relative Risk for excess mortality as compared to reference category; 95% CI: confidence intervals
[c] P-values in univariate and multivariate analyses are from likelihood ratio tests
[d] Multivariate analysis with adjustment for follow up interval 1 to 5 years; in contrast to a standard Cox proportional hazards model, follow up time is not taken as a continuous variable but stratified into intervals
[e] Multivariate analysis with adjustment for follow up and for treatment (three categories: Surgery, Radiotherapy and Surgery+Radiotherapy)

Discussion

This registry-based study addressed age-specific patterns of treatment and survival in patients newly diagnosed with invasive cervical cancer. Age at diagnosis strongly influenced treatment choice, whereas stage of disease and treatment were the most strongly determining factors for survival.
In our study population, the older patients had more advanced disease than the younger patients. The same phenomenon has also been described in other studies and it is considered likely that in the older age group, this can be attributed to patient delay, fewer programmes that provide or promote screening and less compliance with recommended screening practices [7,12,32].

In accordance with the guidelines, most patients received either radiotherapy (31%) or surgery (44%) as single treatment modality. In almost 17% of the cases, surgery revealed indications for post-operative radiotherapy. In total, 4% of the patients did not receive any initial treatment (70+ years: 10%; 50-69 years: 5%; <= 49 years: 1%). The most commonly applied treatment in elderly patients with clinical stage IB-IIA disease was radiotherapy alone. Surgery as a single treatment was the most common in younger patients with stage IB-IIA disease, sometimes with adjuvant radiotherapy. These findings are in agreement with those of other recent studies [17,19]. In contrast with surgery alone and radiotherapy alone, the proportion of patients with stage IB-IIA who received radiotherapy after surgery was almost equal in the three age groups (Figure 1). In this situation, however, RT after surgery will not always have been adjuvant RT. When positive lymph nodes were found during surgery, two scenarios were feasible: 1. Surgery was only explorative and RT was given as the initial treatment. 2. Radical surgery was carried out, followed by post-operative adjuvant RT. This implies that within this treatment group, there were cases with a pathologically proven worse prognosis that received RT as the initial treatment.
We found fairly large differences in treatment choice between patients with early stage disease, but this was not the case in patients with advanced stage disease (FIGO IIB-IVA), the majority of whom were treated with radiotherapy alone, irrespective of their age, which has also been reported by other authors [16,32].

We looked at survival differences by age. Five year relative survival was 81% in women of 49 years or younger, 58% in women aged between 50-69 years and 49% in women of 70 years and older (p=0.00). These percentages are similar to those published in other large series of patients with cervical cancer [32,33]. The poor outcome in the oldest age group was partly related to their unfavourable stage distribution: 5-year survival in stage IB-IIA patients did not differ significantly between the age groups, but it did differ significantly in stage IIB-IVA patients.
To further analyse the effect of age, stage, morphology and treatment on survival, multiple regression analysis was used to estimate relative risks for excess mortality. The results in table 4 illustrate very clearly the interdependency of age, stage and treatment. Age was an important prognostic factor in the model without treatment, but it did not have any significant influence on survival when treatment was included in the model.

However, in observational studies, it is very hard to estimate any real differences in outcomes between groups that received different treatment, because prognostic characteristics will not be equally distributed over the groups [34].
There is general agreement that radical surgery is equally as effective as radical radiotherapy for the treatment of early stage invasive cervical cancer [32]. Therefore the effect of treatment on survival is probably the result of patient selection on specific features/characteristics within the treatment and stage groups such as tumour volume, comorbid conditions and performance status. Unfortunately we did not have any information about these items.
It should be noted that when we calculated relative survival rates, all cases were included. In contrast, the multivariate analysis excluded cases who had not received treatment. Especially elderly patients were highly represented within the latter category.
A population-based study in Sweden [14] revealed lower survival rates in older patients with cervical cancer than in younger patients (period 1960-1984, n=17377), but nothing was mentioned about stage at diagnosis. Although the authors regarded a more advanced stage at diagnosis in older women to be a major cause of the difference in prognosis, they also suggested that a lower proportion of human papilloma virus-associated tumours in older patients independent of stage, might explain the age-related differences in survival because those tumours carry a better prognosis than tumours without any identifiable human papilloma virus nucleic acids. However, the multivariate analyses in our study do not support this hypothesis, because they showed a very low influence of age on survival (besides stage and treatment). Another population-based Scandinavian study performed in Norway [13] reported on 7429 patients diagnosed with cervical cancer (period 1971-1990). Besides studying incidence and mortality trends, they conducted a multivariate analysis on relative survival rates, including stage, time and age. They found that there was a tendency towards a poorer prognosis in younger women, but age was not an important prognostic factor (p=0.08). In a patterns of care study in the US on cervical cancer patients diagnosed in the year 1984 (n=5904) an inverse relationship was found between survival and increasing age at diagnosis which was largely attributed to the unfavourable stage distribution in the elderly [32].
In our study we also looked at survival stratified by histology and age. In contrast with most authors [13,17,35-37], but in concordance with others [16,38] we did not find significant differences in survival between squamous cell carcinoma and adenocarcinoma, either overall or in specific age groups.

We can conclude that the elderly cancer patients in our study were generally treated in accordance with the guidelines, although we did not have any detailed information about symptoms, radiotherapy doses or complications following treatment. Does survival in elderly cervical cancer patients give reasons for concern? We found that relative survival rates differed significantly by age. However, the multivariate analyses on a subset of patients showed that age per se did not have an independent prognostic effect on survival, but that stage and treatment were the explanatory factors. It is very likely that the effect of treatment was due to patient selection based on other characteristics, such as tumour volume, comorbidity and performance status.

Acknowledgement

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5

Influence of age, comorbidity and performance status on the choice of treatment for patients with non-small cell lung cancer: results of a population-based study

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Abstract

Purpose: In the Netherlands in 1997, 43% of patients with newly diagnosed lung cancer were older than 70 years. Large age-specific differences in treatment exist, especially for non-small cell lung cancer. We examined whether age, comorbidity, performance status and pulmonary function influenced treatment according to the prevailing regional guidelines.

Patients and methods: Data on patients with newly diagnosed non-small cell lung cancer (N=803) in the period 1997-1998 in the eastern and southern part of the Netherlands were obtained from the population-based cancer registries of the Comprehensive Cancer Centre East and the Comprehensive Cancer Centre Limburg. Additional data on comorbidity, performance status and pulmonary function (FEV1) were collected, as well as detailed information on initial treatment.

Age-specific differences in treatment according to the guidelines were examined. Adjusted and non-adjusted odds ratios were calculated by means of logistic regression analyses.

Results: 82% of the patients with stage I or II disease received treatment according to the guidelines; this applied to only 48% of the patients with stage IIIA disease and to 54% of the patients with stage IIIB disease. For all stages, this proportion decreased with increasing age. In stage IV disease, 36% of the patients did not receive any treatment; this applied to 52% of the elderly patients (75^+ years). Multivariate analyses only showed associations between comorbidity and treatment choice for the localised stages. No associations were found with performance status. Age of 75^+ years appeared to be the most important factor for not receiving treatment according to the guidelines.

Conclusion: A substantial proportion of elderly patients with non-small cell lung cancer did not receive standard treatment. Performance status and comorbidity seldom formed the underlying reasons for not treating elderly patients according to the guidelines. Calendar rather than biological age seemed to play the most important role in the choice of treatment for patients with non-small cell lung cancer.

Introduction

Lung cancer is a major health problem in the Netherlands, as it is in almost every Western country. Forty-three per cent of patients with newly diagnosed lung cancer are older than 70 years [1]. A previous study showed that more elderly patients with various forms of cancer often did not receive any treatment or received less extensive treatment than their younger counterparts [2].
Large age-specific differences in the diagnostic procedure and treatment methods were especially found in non-small cell lung cancer.
The presence of concurrent health conditions, also known as comorbidities, is seen as one of the most important reasons not to apply the standard therapy. Without comorbidity adjustment, it can be argued that any apparent age bias in decision making is only a reflection of the poorer general health of older patients. In earlier studies, effects were found even after adjusting for comorbidity [3] or performance status [4]. This strongly suggests that physicians are basing their decisions on calendar age rather than on biological age. Population-based studies on age-specific treatment differences in non-small cell lung cancer patients are scarce and very few have addressed several important prognostic factors, such as comorbidity, performance status and pulmonary function in association with the actual treatment received [5]. In the present study, elaborate treatment data (e.g. dose of radiation received) were retrieved from the medical files. While taking into account the regional treatment guidelines, we analysed the influence of age, comorbidity, performance status and pulmonary function on the choice of treatment for non-small cell lung cancer patients.

Patients and Methods

Study population

Data on patients with newly diagnosed non-small cell lung cancer were provided by two regional cancer registries: the cancer registry department of the Comprehensive Cancer Centre East (IKO) for the period 1 January to 1 June 1998 (n=283) and the Maastricht Cancer Registry, department of the Comprehensive Cancer Centre Limburg (IKL) for the period 1 May 1997 to 1 May 1998 (n=520). The total area represented a population of around 2.1 million in 1997. All cases not confirmed to be small cell tumours were considered as being non-small cell lung cancer, including those without histological/cytological confirmation. This means that in some cases the stage could not be defined (stage not applicable).
As this study addressed determinants of treatment choice in a non-selected population, we also included patients whose lung cancer was not their first primary malignancy (15% of the total study group). Registration clerks actively collected data on all the patients from the medical records. In addition to the standard cancer registry items on diagnosis, stage and initial treatment, extensive treatment data were documented, such as the total dose of radiotherapy received, comorbidity, performance status and pulmonary function (Forced Expiratory Volume in 1 second (FEV1)).

Data on comorbidity and performance status were extracted from previous hospital admissions, letters of referral or discharge to general practitioners, the medical history, current medication and preoperative assessments. Comorbidity was recorded using a slightly adapted list of serious diseases developed by Charlson and associates (see Appendix 1) [6]. Having an earlier malignancy also forms part of the Charlson comorbidity index.

Different rating systems are used in oncology to assess performance status, i.e. a patient's functional capacity to work and perform daily activities: the Karnofsky scale [7], the scale described by Zubrod [8] which has been adapted by the Eastern Oncology Group (ECOG) and the World Health Organisation (WHO). The registration clerks recorded all the rating systems used by the specialists; for the analyses, the different scales were translated into the WHO scale (see appendix 2). Although performance status is recognised as being an important prognostic factor in patients with lung cancer [9] this item is not well-documented by physicians. Therefore the registration clerks had to estimate a patient's performance status on the basis of medical history reports written in the medical files by physicians and nurses.

In lung cancer patients, pulmonary function assessment forms part of the standard diagnostic procedure. To estimate the influence of this item, the forced expiratory volume in 1 second (FEV1) and the diffusion capacity for carbon monoxide (DLCO) were recorded. In the analyses, only the FEV1 was used, however, because DLCO was missing in the majority (54%) of cases.

Clinical stage is recorded by the registries according to the current TNM classification system. A new edition of the TNM classification was published in 1997 and became widely available in 1998 [10]. In the present study, however, the 1987 edition [11] with adaptations from 1992 [12] was used, because the prevailing regional treatment guidelines for non-small cell lung cancer, published in 1997 [13] were based on the 1992 TNM classification. The subsequent changes in the TNM classification have already been mentioned. The most important adaptation was that a T3 tumour without positive lymph nodes (N0) was classified as stage IIIA, while in the new version, this is stage IIB.

Patients staged as cMx were not considered to have distant metastases (cM0), provided that T and N were known.

Guidelines valid in the IKL region [13] dated back to April 1997, while those in the IKO region were from 1988 [14]. The guidelines in the two regions were compatible, although those in the IKL region were more specific. The latter definitions were used in our analyses, in order to make differences and variations more visible and concrete.

Table 1 Definitions of treatment according to the guidelines by stage

TNM stage	Intention	Treatment according to the guidelines
Stage I-II (T1-2 N0-1 M0)	Curative	• Surgery, including local excision, lobectomy and pneumectomy • Radiotherapy (RT) 60 Gy (2 Gy fractions) or 51 Gy (3 Gy fractions)
Stage III A (T1-2 N2 M0, T3 N0-2 M0)	Long locoregional control	• Surgery +/- RT • Radiotherapy 60 Gy (2 Gy fractions) or 55 Gy (2.5 Gy fractions) +/- chemotherapy
Stage IIIB (any T N3 M0; T4 any N M0)	Locoregional control	• Surgery +/- RT • Radiotherapy 50 Gy (2 Gy fractions) or 40 Gy (2.5 fractions) +/- chemotherapy
	Palliation	• Radiotherapy 40-49 Gy (2 Gy fractions) or 30-39 Gy (3 Gy fractions)
Stage IV (any T any N M1)	Palliation	• Radiotherapy

On the basis of detailed information on the treatment received in the first three months after diagnosis, we examined whether patients had been treated in accordance with the guidelines (stage I+II, IIIA, IIIB). Treatment definitions per stage according to the guidelines are given in Table 1. For stage IV, we examined which patients received palliative treatment and which patients did not.

Analyses

Adjusted and unadjusted odds ratios for whether or not treatment had been received according to the guidelines were calculated by means of logistic regression analyses (SAS, procedure LOGIST). As treatment guidelines are defined by stage of disease, subgroup analyses were performed for patients with stage I-II, stage IIIA and stage IIIB, and stage IV. Variables included in the models (backwards, alpha 0.05) were age (0-59 years (reference category (ref)), 60-74 years, 75^{+} years), sex, comorbidity (no concomitant disease (ref), 1-2 concomitant diseases, 3 or more concomitant diseases), performance status (0 (ref), 1-2, 3-4, unknown), FEV1 (<2.5 L(ref), >2.5 L, unknown) and Cancer Registry (IKO/IKL). For stage IIIA, a variable for T3 N0 tumour (no positive lymph nodes) was included (yes/no), because of the changes in TNM versions.

Results

The total study population comprised 803 patients with non-small cell lung cancer. Eighty per cent of the patients were male and 20% were female; 51% were aged between 60-74 years and 27% were aged 75 years or older. Table 2 shows some relevant patient characteristics stratified by age group. Proportions of stage IV decreased with increasing age, while proportions of stage unknown or not applicable increased with increasing age.

The proportion of patients with one or more comorbidities increased with increasing age and the proportion of patients with a good performance status was lower among the elderly patients.

Table 2 Patient characteristics NSCLC (1997-1998) stratified by age group

Age (yrs)	<=59	60-74	75+	Total
	N (%)	N (%)	N (%)	N (%)
Sex				
Women	69 (39)	73 (18)	23 (11)	165 (20)
Men	107 (61)	338 (82)	193 (89)	638 (80)
Stage				
I	35 (20)	111 (27)	57 26)	203 (25)
II	4 (2)	3 (1)	3 (1)	10 (1)
IIIA	32 (18)	67 (16)	31 (14)	130 (16)
IIIB	35 (20)	72 (18)	40 (19)	147 (18)
IV	61 (35)	113 (27)	50 (23)	224 (28)
X, NA[a]	9 (5)	45 (11)	35 (16)	89 (11)
Histology				
Large cell carcinoma	48 (27)	77 (19)	35 (16)	160 (20)
Squamous cell carcinoma	51 (29)	168 (41)	100 (46)	319 (40)
Adenocarcinoma	62 (35)	110 (27)	36 (17)	208 (26)
Other[b]	11 (6)	27 (7)	19 (9)	57 (7)
No histological verification	4 (2)	29 (7)	26 (12)	59 (7)
Comorbidity (no)				
0	106 (60)	99 (24)	43 (20)	248 (31)
1	38 (22)	152 (37)	73 (34)	263 (33)
2	16 (9)	86 (21)	48 (22)	150 19)
3≥	4 (2)	54 (13)	42 (19)	100 (12)
Unknown	12 (7)	20 (5)	10 (5)	42 (5)
Performance status				
0	99 (56)	181 (44)	79 (37)	359 (45)
1	20 (11)	80 (19)	53 (24)	153 (19)
2	14 (8)	30 (7)	19 (9)	63 (8)
3	5 (3)	13 (3)	6 (3)	24 (3)
4	2 (1)	5 (1)	3 (1)	10 (1)
Unknown	36 (20)	102 (25)	56 (26)	194 (24)
Region				
IKL	112 (64)	267 (65)	141 (65)	520 (65)
IKO	64 (36)	144 (35)	75 (35)	283 (35)
Total	176(100)	411(100)	216(100)	803(100)

[a] X= unknown (n=27); NA= not applicable ((n=62) (no histology n=59; tumour cells not otherwise specified (NOS) n=3));

[b] Other: tumour cells NOS (n=3); carcinoma NOS (n=32); carcinoma undifferentiated NOS (n=3); pseudosarcomatous carcinoma (n=1); carcinoid NOS (n=6); neuroendocrine carcinoma (n=6); adenosquamous carcinoma (n=6)

Table 3a Patient characteristics stage I-II, IIIA, IIIB NSCLC and distribution of treatment (not) according to the guidelines

	Stage I-II			Stage IIIA			Stage IIIB		
	Not accor. Guidelines N(%)	According Guidelines N(%)	Total N	Not accor. Guidelines N(%)	According Guidelines N(%)	Total N	Not accor. Guidelines N(%)	According Guidelines N(%)	Total N
Age									
<=59 years	1 (3)	38 (97)	39	13 (41)	19 (59)	32	13 (37)	22 (63)	35
60-74 years	15 (13)	98 (86)	114*	31 (46)	35 (52)	67*	28 (39)	44 (61)	72
75+ years	21 (35)	39 (65)	60	22 (71)	9 (29)	31	27 (67)	13 (33)	40
Pulmonary Function (FEV1)									
0.5-1.0 L	3 (25)	9 (75)	12	5 (83)	1 (17)	6	4 (50)	4 (50)	8
1.1-2.4 L	19 (17)	91 (83)	110	30 (45)	36 (55)	66	33 (51)	32 (49)	65
>= 2.5 L	7 (10)	60 (90)	67	17 (47)	19 (53)	36	8 (27)	22 (73)	30
Unknown	8 (35)	15 (65)	23	14 (64)	7 (32)	22*	23 (52)	21 (48)	44
Therapy									
No therapy	24(100)	-	24	21(100)	-	21	45(100)	-	45
Surgery	-	123(100)	123	-	16(100)	16	-	8(100)	8
Radiotherapy (RT)	11 (25)	33 (75)	44	28 (49)	29 (51)	57	13 (18)	58 (82)	71
Surgery+RT	-	19(100)	19	-	8(100)	8	-	4(100)	4
Chemotherapy (CT)	1 (50)	-	2*	9(100)	-	9	9(100)	-	9
RT+CT	1(100)	-		2 (17)	10 (83)	12	-	9(100)	9
S+CT/S+RT+CT	-	-		6(100)	-	6	1(100)	-	1
Comorbidity (number)									
0	2 (3)	54 (95)	57*	21 (51)	20 (49)	41	18 (34)	35 (66)	53
1	13 (18)	60 (82)	73	25 (54)	21 (46)	46	26 (59)	18 (41)	44
2	11 (23)	36 (77)	47	6 (43)	8 (57)	14	12 (46)	14 (54)	26
3≥	8 (27)	22 (73)	30	10 (50)	9 (45)	20*	8 (42)	11 (58)	19
Unknown	3 50)	3 (50)	6	4 (44)	5 (56)	9	4 (80)	1 (20)	5
Performance status									
0	16 (12)	110(87)	127*	27 (45)	34 (55)	62*	22 (37)	38 (63)	60
1	5 (16)	26 (84)	31	16 (50)	16 (50)	32	20 (56)	16 (44)	36
2	3 (60)	2 (40)	5	5 (71)	2 (29)	7	6 (37)	10 (63)	16
3-4	-	-	-	5 (83)	1 (17)	6	3 (75)	1 (25)	4
Unknown	13 (26)	37 (74)	50	13 (56)	10 (44)	23	17 (55)	14 45)	31
Comprehensive Cancer Centre									
IKL	24 (16)	124(83)	149*	41 (54)	34 (45)	76*	42 (47)	48 (53)	90
IKO	13 (20)	51 (80)	64	25 (46)	29 (54)	54	26 (46)	31 (54)	57
Total	37 (17)	175(82)	213(100)	66 (51)	63 (48)	130(100)	68 (46)	79 (54)	147

* Treatment of one patient was unknown

Stage I-II

In the patients with stage I or II disease, 82% received treatment according to the guidelines, i.e. surgery or radiotherapy (Tables 1 and 3a). However, the proportions decreased with increasing age, from 97% in the age group 59 years and younger, to 86% in the age group 60-74 years and to 65% in the age group 75 years and older.
Surgical procedures (n=142) were lobectomy (64%), pneumectomy (31%) and smaller resections (5%) (data not shown). In this group, 95% of the patients without any serious concomitant diseases and 73% of the patients with three or more concomitant diseases were treated according to the guidelines. More patients with a good performance status (WHO grade 0) received treatment according to the guidelines then patients with a poorer performance status (WHO grade 1-2). In a logistic regression model, the factor age of 75 years or older was associated with higher proportions of patients who did not receive treatment according to the guidelines (OR=8.5; 95% CI 2.2-32). Also the presence of comorbidity appeared to significantly influence the treatment of this group of lung cancer patients (Table 5). After adjusting for the other variables, ORs for performance status were no longer significantly increased.

Table 3b Patients with NSCLC not treated according to the guidelines (stage I-II, IIIA, IIIB)

	Age			
	<= 59 years N (%)	60-74 years N (%)	75+ years N (%)	Total N (%)
Stage I-II				
No therapy		9 (60)	15 (71)	24 (65)
RT < 60 Gy (2 Gy fractions) or < 51 Gy (3 Gy fractions)	1(100)	4 (27)	6 (29)	11 (30)
CT/RT+CT	-	2 (13)	-	2 (5)
Subtotal	1(100)	15(100)	21(100)	37(100)
Stage III A				
No therapy	4 (31)	5 (16)	12 (55)	21 (16)
RT < 60 Gy (2 Gy fractions) or < 55 Gy (2.5 Gy fractions)	2 (15)	17 (55)	9 (41)	28 (42)
Chemotherapy (CT)	2 (15)	6 (19)	1 (4)	9 (14)
Surgery (S)+CT	2 (15)	2 (6)	-	4 (6)
Radiotherapy (RT)+CT	2 (15)	-	-	2 (3)
S+RT+CT	1 (8)	1 (3)	-	2 (3)
Subtotal	13(100)	31(100)	22(100)	66(100)
Stage IIIB				
No therapy	6 (46)	16 (57)	23 (85)	45 (66)
Radiotherapy < 30Gy	1 (8)	9 (32)	3 (11)	13 (19)
Chemotherapy	6 (46)	2 (7)	1 (4)	9 (13)
S+RT+CT	-	1 (4)	-	1 (2)
Subtotal	13(100)	28(100)	27(100)	68 (100)

Stage III A

About 48% of the patients with stage IIIA NSCLC received treatment according to the guidelines, i.e. surgery with or without radiotherapy, radiotherapy alone or in combination with chemotherapy (Table 1 and 3a). More patients aged 75 years and older had not been treated according to the guidelines (71%) than their younger counterparts. In the univariate as well as the multivariate analyses, age was the most important risk factor for not receiving treatment according to the guidelines (Table 5). The presence of one or more comorbidities, or other variables such as performance status and pulmonary function did not show any significant association with not receiving treatment according to the guidelines. In patients without positive lymph nodes (T3N0) the risk of not being treated according to the guidelines was significantly lower than in the other categories of stage IIIA (OR 0.08, 95% CI: 0.03-0.33).

Stage IIIB

Fifty-four per cent of the patients with stage IIIB disease received treatment according to the guidelines, i.e. surgery, radiotherapy, a combination of the two, or RT with chemotherapy (Table 1). In patients aged 75 years and over, this proportion was lower: 33% (Table 3a). The large majority (73%) of stage IIIB patients who were treated according to the guidelines received radiotherapy alone; 29 out of these 58 patients received a palliative dose (not shown). In the univariate analysis, age of 75 years and over, pulmonary function (FEV1 < 2.5 L or unknown) and the presence of one or two comorbidities showed a significantly higher risk for not receiving treatment according to the guidelines (Table 5). However, in the multivariate analyses, none of these factors remained significantly associated with the risk of not being treated according to the guidelines.

Stage I+II, IIIA, IIIB, treatment not according to the guidelines

Table 3b shows the patients with stage I+II, IIIA and IIIB who had not been treated according to the guidelines: 37 patients with stage I-II NSCLC had not been treated according to the guidelines and 24 had not received any treatment, all of them were 60 years or older. Radiotherapy with less than a total dose of 60 Gy (2 Gy fractions) or 51 Gy (2.5 Gy fractions) had been received by 11 patients, whereas one patient had received RT in combination with chemotherapy and one patient had been treated with chemotherapy alone.

Fifty-one per cent of the stage IIIA patients did not receive treatment according to the guidelines. In this group, 28 patients had received radiotherapy alone, but a total dose of less than 60 Gy (2 Gy fractions) or 55 Gy (2.5 Gy fractions); 17 patients received chemotherapy with or without another modality, but not according to the guidelines, while 21 patients (16%) did not receive any treatment. In contrast with stage IIIA, a large proportion of the stage IIIB patients were not treated at all (66%) and this percentage increased with increasing age. Treatment consisted of radiotherapy with a dose of less than 30 Gy (19%) or chemotherapy (13%).

Stage IV

In the years 1997 and 1998 there was no clear standard treatment for stage IV NSCLC. Survival rates were low and treatment was administered for palliative purposes. Table 4a shows the proportions of patients who received treatment and those who did not. No treatment had been applied to 36% (n=76) of the patients. This proportion differed by age group: 20% of the patients aged 59 years or younger had not been treated, 34% of the patients aged 60-74 years and 52% of those aged 75 years or older. Patients who had been treated mostly received radiotherapy (n=94) or chemotherapy (n=30) (Table 4a). Table 4b presents treatment by age and whether radiotherapy was locoregional, to metastases, or both. The proportion of patients that received radiotherapy to metastases decreased with increasing age: 43% of the patients aged 59 years or younger, 26% of the patients aged 60-74 years and 18% of the patients aged 75 years and over. Chemotherapy was mostly administered to younger patients and consisted of regimens with gemcitabine.
Logistic regression analysis for whether or not treatment had been received revealed that an age of 75 years or older and an FEV1 of lower than 2.5 L or FEV1 unknown was related to not receiving treatment.

Stage unknown/ not applicable

Twenty-seven patients had stage unknown because of an incomplete diagnostic procedure and in 62 patients there was no histological classification, which means that their stage could not be defined. In this group, 80 out of the 89 patients were aged 60 years and older. The majority (54%) had not received treatment and this proportion increased with increasing age: 33% of the patients aged 59 years and younger, 49% of the patients aged 60-74 years and 66% of those aged 75 years and over. In the total group who received treatment (n=41), 15% underwent surgery and 25% received radiotherapy (results not shown).
Logistic regression analyses (results not shown) indicated that the factors age 75 years or older (OR 2.9; 95% CI:1.3-6.6), performance status of WHO 3-4 (OR 2.4; 95% CI:1.0-6.0) or unknown pulmonary function (OR 3.4; 95% CI:1.5-7.3) were associated with stage unknown or the absence of histological classification.

Table 4a Patient characteristics stage IV NSCLC, treatment or no treatment

	Stage IV			
	No treatment	Treatment	Treatment unknown	Total
Age				
<=59 years	12 (20)	48 (79)	1 (2)	61
60-74 years	38 (34)	72 (64)	3 (3)	113
75+ years	26 (52)	22 (44)	2 (4)	50
Pulmonary Function (FEV1)				
0.5-1.0 L	3 (43)	4 (57)	-	7
1.1-2.4 L	32 (36)	54 (61)	3 (3)	89
≥2.5 L	4 (12)	28 (85)	1 (3)	33
Unknown	37 (39)	56 (59)	2 (2)	95
Therapy				
No therapy	76(100)	-	-	76
Surgery	-	4(100)	-	4
Radiotherapy (RT)	-	94(100)	-	94
Surgery+RT	-	3(100)	-	3
Chemotherapy (CT)	-	30(100)	-	30
RT+CT	-	11(100)	-	11
Unknown	-	-	6(100)	6
Comorbidity (no)				
0	25 (32)	53 (67)	1 (1)	76
1	26 (37)	44 (63)	-	70
2	14 (33)	26 (62)	2 (5)	42
3≥	6 (33)	11 (61)	1 (6)	18
Unknown	5 (33)	8 (53)	2 (14)	15
Performance status				
0	26 (32)	55 (68)	-	82
1	12 (29)	29 (71)	-	40
2	11 (41)	16 (59)	-	27
3-4	5 (33)	10 (67)	-	15
Unknown	22 (37)	32 (53)	6 (10)	59
Comprehensive Cancer Centre				
IKL	47 (33)	90 (64)	4 (3)	141
IKO	29 (35)	52 (63)	2 (2)	83
Total	76 (34)	142 (63)	6 (3)	224(100)

Table 4b Treatment for stage IV NSCLC by age

	Age			
	<= 59 years	60-74 years	75+ years	Total
Treatment	N (%)	N (%)	N (%)	N (%)
No treatment	12 (20)	38 (34)	26 (52)	76 (34)
Surgery	1 (2)	3 (3)	-	4 (2)
Radiotherapy (RT) locoregional	6 (10)[a]	12 (11)	4 (8)	22 (10)
Radiotherapy metastases	26 (43)[b]	30 (26)	9 (18)	65 (29)
Radiotherapy both	4 (6)[c]	10 (9)	4 (8)	18 (8)
Chemotherapy	11 (18)	15 (13)	4 (8)	30 (13)
Unknown	1 (1)	5 (4)[d]	3 (6)	9 (4)
Total	61 (27)	113 (50)	50 (22)	224(100)

[a] one patient received RT + chemotherapy

[b] one patient received Surgery + RT and 5 patients received RT + chemotherapy

[c] one patient received S + RT

[d] two patients received RT but the localisation and dose was unknown

Table 5 Adjusted and unadjusted Odds Ratios (OR) with 95% confidence interval ( ) for treatment of NSCLC not according to the guidelines (stage I-II, IIIA, IIIB) and for no treatment (stage IV)

	Stage I-II		Stage IIIA		Stage IIIB		Stage IV	
	Unadj. OR	Adj. OR	Unadj. OR	Adj. OR	Unadj. OR	Adj. OR	Unadj. OR	Adj. OR
Age								
<= 59 Years	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1(ref)
60-74 years	3.2 (0.9-11)	2.2 (0.6-8.1)	1.3 (0.6-3.0)	1.2 (0.4-3.4)	1.1 (0.5-2.5)	0.8 (0.3-2.1)	2.1 (1.0-4.4)	2.1 (0.9-5.0)
75+ years	12.8 (3.5-46)	8.5 (2.2-32)	3.6 (1.2-10)	3.9 (1.1-14)	3.5 (1.3-9.1)	2.2 (0.7-6.8)	4.7 (2.0-11)	5.1 (2.0-13)
Pulmonary Function (FEV1)								
< 2.5 L	1.5 (0.7-3.1)	1.0 (0.5-2.3)	1.1 (0.5-2.3)	0.9 (0.3-2.6)	2.8 (1.1-7.1)	2.3 (0.8-6.2)	4.2 (1.4-13)	3.9 (1.2-12)
>= 2.5 L	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Unknown	2.4 (0.9-6.8)	2.4 (0.7-8.3)	2.2 (0.7-6.8)	2.5 (0.6-10)	3.0 (1.1-8.2)	1.9 (0.6-5.8)	4.6 (1.5-14)	4.7 (1.4-15)
Comorbidity								
0	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1-2	6.5 (2.2-19)	4.8 (1.5-15)	1.0 (0.5-2.3)	1.3 (0.5-3.2)	2.3 (1.1-4.8)	1.9 (0.8-4.4)	1.2 (0.6-2.2)	0.8 (0.4-1.7)
3≥	8.2 (2.4-28)	5.7 (1.5-21)	0.9 (0.3-2.5)	0.7 (0.2-2.2)	1.9 (0.7-5.1)	1.3 (0.4-4.0)	1.2 (0.5-3.0)	0.7 (0.3-1.8)
Performance Status								
0	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1-2	3.1 (1.4-6.8)	2.1 (0.9-4.9)	1.5 (0.6-3.3)	1.8 (0.7-4.6)	1.7 (0.8-3.7)	1.5 (0.7-3.4)	1.1 (0.5-2.1)	0.9 (0.4-1.8)
3-4	-	-	6.3 (0.7-57)	2.9 (0.3-30)	5.2 (0.5-52)	5.3 (0.4-64)	1.1 (0.3-3.4)	0.9 (0.2-3.3)
Unknown	1.2 (0.5-2.6)	0.8 (0.3-1.9)	1.6 (0.6-4.3)	1.5 (0.5-4.9)	2.1 (0.9-5.1)	2.1 (0.8-5.7)	1.4 (0.7-3.0)	1.3 (0.6-2.8)
TNM T3N0								
Yes	Not Applicable		0.1 (0.0-0.4)	0.08 (0.0-0.3)	Not applicable		Not applicable	
No			1 (ref)	1 (ref)				
Comprehensive Cancer Centre								
IKO	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
IKL	1.1(0.5-2.0)	#	0.7 (0.3-1.4)	#	0.9 (0.4-1.9)	#	1.1 (0.6-1.9)	#

variable not included in the final model

Discussion

The present retrospective study investigated treatment patterns for non small-cell lung cancer patients in the eastern and southern part of the Netherlands. Less than half the patients with a stage I, II, IIIA or IIIB disease (44%) were treated according to the guidelines. Adherence to treatment guidelines was highest in stages I-II and decreased with increasing age. The majority of patients with stage IV disease received palliative treatment for palliation (63%), but the proportions varied by age group: 79% in the age group 59 years and younger, 64% in the age group 60-74 years and 44% in the age group 75 years and over.
After adjustment for the effect of age and cancer stage, the influences of comorbidity and performance status on treatment choice were less than expected. In the univariate analyses, significant associations with comorbidity and performance status were only found for the localised stages. Poor pulmonary function (FEV1) was associated with not receiving palliative treatment in stage IV patients, even after adjustment for age, comorbidity and performance status.

Several factors should be considered when interpreting these findings. First, comorbidity data, performance status and pulmonary function (FEV1) were not part of the standard registration items at the time of data collection (comorbidity was included in 1999). This means that registration clerks were not used to documenting these items. To record comorbidity, methods introduced by the adjacent cancer registry in Eindhoven (IKZ) were used. They have been recording comorbidity since 1993 and a validation project has been carried out [3]. To evaluate the data on comorbidity in the present study, the prevalence of comorbidity in lung cancer patients was compared to the outcomes of the IKZ study [3]. Differences were in a range of 1 to 6% for both men and women in seven out of eight categories.
Second, even though great effort was made, information on performance status and FEV1 was difficult to obtain from the medical files. In 14% of the cases it was clear that no FEV1 test had been performed, while in 12% of the cases the notes in the medical files were not clear about the performance of pulmonary function tests. In both categories, the performance status was coded as unknown (percentage by age group: <= 59 years: 20%, 60-74 years: 25% and 75+ years: 26%).

Comorbidity significantly influenced treatment for the early stage non-small cell lung cancer. This might be related to the fact that the prevalence of comorbidity in patients with a stage I-II NSCLC was higher than that in patients with more advanced lung cancer (Table 2). This phenomenon was also found by Janssen-Heijnen et al [3], who ascribed it to screening bias, e.g. lung cancer was diagnosed at an early stage as a result of regular monitoring of other chronic diseases. This might also explain the high proportion of elderly patients with stage I-II at diagnosis, although this could be partly the result of understaging due to less extensive diagnostic procedures [2].
In the present study, stage was classified according to the 'old' TNM classification [12]. In the new TNM classification [10], cases with T3N0 (no positive lymph nodes) are classified as IIB instead of IIIA. This change in TNM classification was made because apparently, these patients have better survival and should be offered treatment with curative intent.

In the present study, T3N0 patients were analysed in more detail, because physicians may have been aware of the more favourable prognosis and have treated them according to the new staging classification [15]. Compared to the other stage IIIA patients, more T3N0 patients had been treated according to the guidelines. A fairly large proportion of the other stage IIIA patients had received radiotherapy to a lower total dose than advised in the guidelines (n=28), or they had received no treatment at all (N=21); the majority of the latter patients were aged 60 years and older.
There are no curative treatment options for patients with metastasised lung cancer (stage IV). Radiotherapy administered for palliation of severe respiratory symptoms or for metastases causing severe complaints was a generally accepted treatment policy. Therefore the characteristics of the patients who received such treatment (to prolong survival or for symptomatic relief) were compared to those of the patients who did not receive any treatment. This comparison revealed different proportions by age group: 44% of the patients aged 75 years and over received some kind of palliative treatment, mostly radiotherapy, whereas this was 64% in the age group 60-74 years and 79% in patients aged 59 years and younger. Relatively fewer elderly patients received radiotherapy for metastases.

Clinicians who managed elderly patients with lung cancer may have felt cautious about referring them for radiotherapy. In the study period 1997-1998, research specifically performed to assess the problems and benefits of radiotherapy for lung cancer in elderly patients was scarce [16]. Patterson et al retrospectively studied 149 lung cancer patients aged 75 years and over. They concluded that palliative radiotherapy was well tolerated and the response was similar to that in younger patients. Other studies have also indicated that (radical) radiotherapy can be applied to elderly people without increased toxicity [17-20]. However, heterogeneity among individuals increases with increasing age, and more than in younger cancer patients, all therapeutic options should be considered in relation with careful evaluation of the patient (functional assessment, comorbidities, stage of disease, social situation, individual wishes for therapy, etc.) [21,22]. Another positive development over the past few years is that most clinical trials no longer specify upper age limits. Unfortunately the recruitment of elderly patients in trials is still low [23].
Especially in the younger age groups with advanced stage NSCL, chemotherapy seemed to occupy a fairly important position in the treatment options; 30 patients received chemotherapy alone and 11 received both radiotherapy and chemotherapy. At time of the study, 1997-98, the role of chemotherapy in stage IV NSCLC in everyday practice was still uncertain and did not form part of the IKL or IKO treatment guidelines. However, in 1995, the results of a meta-analysis on randomised trials revealed an increase in median survival of about 6 weeks and a 10% improvement in 1-year survival compared to patients managed with supportive care only [24]. In subsequent years it has become clear that several chemotherapy regimens could offer a small increase in 1-year survival and a delay in symptoms that cause quality of life deterioration in elderly and unfit patients [25]. These developments led to changes in the IKL treatment guideline [26] by making chemotherapy part of the standard treatment, although it is still advised to do this in trial settings.

In the present study, performance status did not seem to play a major role in treatment choice, which is in agreement with Brown et al [4] who studied differences in treatment for 563 lung cancer patients in the UK. We found that performance status as such was often not even mentioned in medical files. Besides, the percentage of patients with a very poor performance status (3-4), was low. Only 4% had a performance status of 3-4 (proportions were higher in patients with stage IV (7%) and stage unknown (10%)).

Our study population included 89 patients with unknown stage, partly because of less extensive diagnostic procedures (N=27) and partly because the diagnosis was not histologically confirmed (N=62). The high prevalence of comorbidities and the poor performance status of these patients may indicate that the diagnostic procedure was less extensive because of comorbid conditions or low performance status which implicitly meant that patients were not considered to be candidates for standard treatment. In some cases, this may have been the result of the misunderstanding that extensive clinical staging in the elderly is not worthwhile [27]. It seems likely that from the very beginning of the diagnostic process, there was no intention to treat these patients according to the guidelines. Obviously, there will sometimes be very good reasons not to perform extensive diagnostic procedures, or not to treat a patient according to the standard guidelines (e.g. lower RT dose). From the documentation of the reasons for treatment choice, it was learned that occasionally the disease was progressing too rapidly or sometimes the treatment-related complications were considered unacceptable. Nevertheless, in the literature there are strong indications that a nihilist approach from physicians plays an important role [28] and that the number of patients who refuse treatment is very small [29].

In the present study, the calendar age of the patient was the most important factor upon which physicians based their therapy decision. Fairly large proportions of elderly patients were not treated, were undertreated or were withheld some form of treatment for palliation. Exclusion of elderly patients from former cancer trials and lack of data concerning the benefit of treatment for elderly patients with cancer may have played a role in treatment decisions.

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Appendix 1

Classification of co-morbidity, according to an adapted version of the list developed by Charlson et al. (1987)

COPD
Cardiovascular disease (myocardial infarction, cardiac decompensation, angina pectoris, intermittent claudication, abdominal aneurysm)
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Other malignancies (except for basal cell skin carcinoma)
Hypertension
Diabetes Mellitus (medically treated)
Other:
Soft tissue diseases (Besnier Boeck disease (sarcoidosis), Wegener's granulomatosis, SLE (systemic lupus erythematosis)
Rheumatoid arthritis (only severe)
Kidney diseases (chronic glomerulonephritis, chronic pyelonephritis)
Bowel diseases (Crohn's disease, ulcerative colitis)
Liver diseases (cirrhosis, hepatitis)
Dementia
Tuberculosis

Appendix 2

WHO (Zubrod) scale

0	Normal activity
1	Symptoms, but nearly fully ambulatory
2	Some bed rest, but needs to be in bed for less than 50% of normal daytime
3	Needs to be in bed for more than 50% of normal daytime
4	Unable to get out of bed

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6

Cancer in the very elderly Dutch population

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Abstract

Background: Cancer incidence and mortality rates rarely are studied in people age >= 85 years. Usually, patients ages 65 years, 75 years, and 85 years of age are combined into 1 group, because of small numbers. The number of people age ≥ 85 years in the Netherlands increased from 99,000 in 1976 to 203,000 in 1995 (an increase of 105%). The growth of the total population in this period was only 13%. This study addressed cancer incidence and mortality rates among the very elderly in the Netherlands.

Methods: Cancer mortality data (1976-1995) and population data were obtained from Statistics Netherlands, whereas cancer incidence data (1989-1995) were provided by the Netherlands Cancer Registry. Cancer incidence and mortality rates were calculated and trends in cancer mortality were studied.

Results: Total cancer incidence rates were highest in the age group 85-94 years, in men and women (3466/100,000 person-years and 1604/100,000 person-years, respectively). Prostate carcinoma was the most frequent cancer in men ages 85-94 years, followed by colorectal carcinoma. In women ages 85-94 years, colorectal carcinoma was most frequent, closely followed by breast carcinoma. In the 95+ years age group squamous cell skin carcinoma was the most frequent cancer in both men and women, followed by prostate carcinoma in men and breast carcinoma in women. Cancer mortality rates increased with increasing age to nearly 3700/100,000 person-years in men age 95+ years and to 2500/100,000 person-years in women age 95+ years. In men, lung carcinoma was the most frequent cancer-related cause of death in patients age ≤ 85 years, whereas in older men this applied to prostate carcinoma. In women, breast cancer was the most frequent cancer-related cause of death in all age groups above 55 years. Cancer as a cause of death became less prominent with increasing age. Over the period 1991-1995, 42% of deaths in men ages 55-64 years were attributed to cancer versus 52% of deaths in women (total population); these proportions in the 95+ years age group were 11% and 7%, respectively.

Conclusions: Peak incidence rates of major cancers were found in the very elderly population in the Netherlands. Different trends in age-specific mortality rates of individual cancer sites were found, with stable rates in the middle age groups and increasing rates in the oldest age groups. This may reflect a real increase caused for instance by changes in mortality from other diseases and/or an artifactual increase caused by increased cancer detection rates in the (very) elderly.

Introduction

In the Netherlands, the number of persons age ≥ 85 years increased from 99,000 in 1976 to 203,000 in 1995 (an increase of 105%). It is predicted that by the year 2015 the total population living in the Netherlands will have increased by 8.4%, from 15.4 million in 1994 to 16.7 million [1]. However, the segment of the population age 65+ years is expected to grow much faster (45%), although the proportion of persons age ≥ 85 years will remain the same.
In 1995, > 5% of all new male and nearly 8% of all new female cancer cases in the Netherlands were diagnosed in patients age ≥ 85 years [2]. Because cancer predominantly is a disease related to old age, the number of cancer cases can be expected to increase dramatically in the future. Compared with 1994, an overall increase has been predicted in the absolute numbers of patients with cancer of common sites such as colon, lung, breast and prostate for the year 2015, varying from 30-60% [3].
Cancer incidence rate and mortality studies often present numbers and rates for "the elderly" in patients age 85+ years or 75+ years, and sometimes even as young as 65+ years. The main reason for this is the small numbers or unavailability of more detailed data. The increasing number of very elderly people, sometimes referred to as the "oldest old", created the opportunity to divide cancer incidence and mortality rates into distinct age categories in patients ages 85-94 years and in patients age ≥ 95 years. The current study presents cancer incidence rates and cancer mortality rates in the very elderly population in the Netherlands.

Materials and methods

Incidence data

Incidence data regarding persons age ≥ 55 years for the years 1989-1995 were provided by the population-based Netherlands Cancer Registry, for which 9 regional cancer registries collect data. All invasive and in situ malignancies, including noninvasive bladder carcinoma diagnosed from 1989 onwards in people living in the Netherlands, have been registered nationwide [4]. We studied only invasive tumors; in situ bladder tumors (Tis) and papillary noninvasive bladder tumors (T_A) were not included.
Due to privacy regulations and the absence of a personal identification number, death certificates cannot be used as an additional source of notification of cancer cases in the Netherlands. Despite the lack of this notification source, the infrastructure of the Netherlands health care system and the notification procedures used have made it possible to establish a cancer registry with high completeness (96.2%), also in the highest age groups [5,6].
In the case of multiple tumors, the same rules were applied as those recommended by the International Association of Cancer Registries [7]. In brief, a tumor only is included in the incidence rates if the localization (based on the first three numbers of the 9th revision of the International Classification of Diseases (ICD-9) or the histology (divided into eight groups) is different from the other tumors in the same patient. Lateralization and the time between the development of the first and second tumors do not play a role.

Mortality data

Cancer mortality data were provided by Statistics Netherlands. This organization receives mortality data from death certificates that are filled in by physicians. For the period 1976-1995, we received data concerning the number of deaths in the Netherlands with the underlying causes of death coded according to the ICD-9 (malignancies: 140-208) and subdivided by gender, 5-year age categories (ranging from birth-4 years to 100$^+$ years), and date of death (1976-1980, 1981-1985, 1986-1990, 1991-1995).

Population data

Annual population data by gender and 5-year age categories (ranging from birth-4 years to 100$^+$ years) for the period 1976-1995 also were provided by Statistics Netherlands. Highly reliable population data can be obtained from Statistics Netherlands because all demographic changes are recorded at the municipal level. In 1976, the Netherlands had an average population of 13.7 million (6.8 million males and 6.9 million females). In 1995 the average population had grown to 15.4 million (7.6 million males and 7.8 million females). Although the birthrates dropped to the European average after 1970, the Dutch population is still relatively young compared to other European countries (48% of individuals are between 15-44 years of age). However, the number of people age $\geq$ 65 years is growing rapidly (1.3% annually compared with an annual growth of 0.6% during the last decade).
Approximately 9% of the population is comprised of ethnic minorities (mainly from Indonesia, Surinam, the Netherlands Antilles, Turkey and Morocco). Life expectancy in the Netherlands is among the highest in the world; during the period 1991-1995 it was 74.3 years for males and 80.2 years for females.

Analyses

Using the average population in 5 age groups (55-64 years, 65-74 years, 75-84 years, 85-94 years and 95$^+$ years) in the separate periods, the age-specific incidence and mortality rates were calculated as the annual number of new cases or deaths per 100,000 individuals in that age group.
Furthermore, we calculated proportions of cancer as a cause of death in proportion to other causes of death in the different age categories. Due to the privacy regulations mentioned earlier, the provision of mortality data from Statistics Netherlands on the individual level is restricted. Therefore, the proportions refer to the total population in the age categories concerned, not only to the patients with cancer.

Table 1a The 10 most frequent cancer sites (ICD-9) in males according to age group in the Netherlands between 1989-1995: Absolute numbers (N) and incidence rates (Number/100,000 person-years)

	55-64 years			65-74 years			75-84 years			85-94 years			95+ years		
Rank	Site	N	Rate	Site	N	Rate	Site	N	Rate	Site	N	Rate	Site	N	Rate
1	Lung (162)	12448	255.1	Lung(162)	19940	566.9	Prostate (185)	13212	808.5	Prostate (185)	3223	938.4	Skin*(173)	94	570.9
2	Colorectal (153-154)	5593	114.6	Prostate (185)	14004	398.1	Lung(162)	12111	741.2	Colorectal (153-154)	1545	449.9	Prostate (185)	82	498.0
3	Prostate (185)	4797	98.3	Colorectal (153-154)	9019	256.4	Colorectal (153-154)	7087	433.7	Lung(162)	1469	427.7	Colorectal (153-154)	48	291.5
4	Bladder(188)	2230	45.7	Bladder (188)	4145	117.8	Skin*(173)	3562	218.0	Skin*(173)	1352	393.7	Bladder(188)	36	218.6
5	Stomach (151)	2144	43.9	Stomach (151)	3689	104.9	Bladder (188)	3265	199.8	Bladder(188)	808	235.3	Stomach (151)	22	133.6
6	Unknown Primary(199)	2076	42.5	Skin(173)*	3578	101.7	Stomach (151)	2973	181.9	Stomach (151)	712	207.3	Lung(162)	18	109.3
7	Kidney(189)	1713	35.1	Unknown Primary (199)	3300	93.8	Unknown Primary (199)	2323	142.2	Unknown Primary (199)	528	153.7	Unknown Primary(199)	13	79.0
8	Skin(173)	1680	34.4	Kidney (189)	2323	66.0	Kidney (189)	1347	82.4	Leukemia (204-208)	300	87.4	Lymphoma (200-202)	11	66.8
9	Lymphoma (200-202)	1427	29.2	Lymphoma (200-202)	1906	54.2	Lymphoma (200-202)	1201	73.5	Lymphoma (200-202)	262	76.3	Leukemia (204-208)	10	60.7
10	Larynx (161)	1315	26.9	Pancreas (157)	1695	48.2	Pancreas (157)	1174	71.8	Pancreas (157)	237	69.0	Gallbladder (156)	5	30.4

ICD: International Classification of Diseases

* Skin cancer other than melanoma and basalioma (mainly squamous cell carcinoma)

Table 1b The 10 most frequent cancer sites (ICD-9) in females according to age group in the Netherlands between 1989-1995: Absolute numbers (N) and incidence rates (Number/100,000 person-years)

	55-64 years			65-74 years			75-84 years			85-94 years			95+ years		
Rank	Site	N	Rate	Site	N	Rate	Site	N	Rate	Site	N	Rate	Site	N	Rate
1	Breast(174)	13724	270.5	Breast(174)	14400	325.1	Breast(174)	10711	351.0	Colorectal (153-154)	2950	321.1	Skin*(173)	165	305.7
2	Colorectal (153-154)	4567	90.0	Colorectal (153-154)	8088	182.6	Colorectal (153-154)	8734	302.8	Breast(174)	2940	320.0	Breast(174)	94	174.2
3	Lung(162)	3234	63.7	Lung(162)	3326	75.1	Unknown Primary (199)	2410	84.4	Skin*(173)	1504	63.7	Colorectal (153-154)	91	168.5
4	Uterus(182)	2431	47.9	Uterus(182)	2833	63.9	Stomach (151)	2219	78.1	Unknown Primary (199)	944	102.8	Stomach (151)	42	77.8
5	Ovary(183)	2053	40.5	Ovary(183)	2525	57.0	Skin*(173)	2119	75.3	Stomach (151)	903	98.3	Unknown Primary (199)	39	72.3
6	Unknown Primary (199)	1251	24.7	Unknown Primary (199)	2049	46.3	Uterus(182)	1915	66.5	Pancreas (157)	537	58.5	Lymphoma (200/202)	20	40.8
7	Melanoma (172)	1066	21.0	Stomach (151)	1615	36.5	Ovary(183)	1616	58.2	Lymphoma (200-202)	530	57.7	Pancreas (157)	19	35.2
8	Kidney(189)	992	19.5	Lymphoma 200/202	1604	36.2	Lung(162)	1612	58.0	Uterus(182)	497	54.1	Melanoma (172)	16	29.6
9	Lymphoma (200-202)	990	19.5	Skin*(173)	1577	35.6	Lymphoma (200-202)	1516	53.7	Bladder (188)	464	50.5	Bladder (188)	16	29.6
10	Stomach (151)	853	16.8	Pancreas (157)	1450	32.7	Pancreas (157)	1574	52.9	Ovary(183)	384	41.8	Gallbladder (156)	15	27.8

ICD: International Classification of Diseases

* Skin cancer other than melanoma and basalioma (mainly squamous cell carcinoma)

Results

Cancer Incidence

During the 7-year study period (1989-1995), 335,156 incident cases of invasive cancer were reported in Dutch people age ≥ 55 years. A total of 27,633 cases (8.2%) occurred in persons age ≥ 85 years and nearly 1000 (0.3%) were age 95⁺ years. The annual incidence rate for all cancer sites combined reached a peak at the age of 85 years and decreased thereafter (Fig. 1). In women ages 85-94 years, this rate was 1604/100,000; in men this rate was nearly 3500/100,000.

Tables 1A and 1B show the ten most frequent cancer sites in males and females according to age category in the registration years 1989-1995. In men (Table 1A), prostate, lung and colorectal carcinoma were the three most frequent malignancies, although in different ranking order. In the 95⁺ years group, squamous cell skin cancer was the most frequent whereas prostate carcinoma was the second, colorectal carcinoma the third, and lung carcinoma the sixth most frequent.

In women (Table 1B) breast carcinoma was the most frequent malignancy in the 55-64 years, 65-74 years, and 75-84 years age groups, followed by colorectal carcinoma. In women ages 85-94 years, colorectal carcinoma passed breast carcinoma with only a very small difference. Squamous cell skin carcinoma climbed in rank with increasing age; in the 95⁺ years group, this malignancy was the most frequent, whereas breast cancer was the second and colorectal carcinoma the third most frequent. In the younger age groups (55-64 years and 65-74 years) lung carcinoma was third most frequent, whereas in the older age groups, lung carcinoma was not in the 'top ten'. We found that in the two oldest age groups, unknown primary tumors ranked high, as fourth and fifth most frequent, respectively. In addidtion, tumors of the pancreas and bladder appeared to be more common in the oldest age groups, with incidence rates that were similar to, for example, gynecologic malignancies in younger women (rates of between 30-60/100,000).

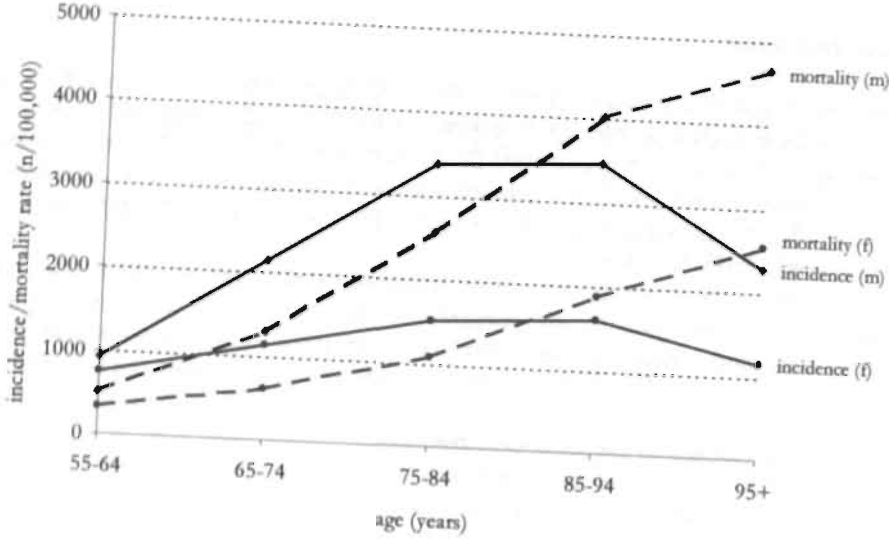

Figure 1 Annual age-specific cancer incidence and mortality rates by gender; data derived from Netherlands Cancer Registry, 1989-1995 and Statistics Netherlands 1991-1995; m: male; f: female

Figure 2 shows age-specific incidence rates of the most common cancers in males (Fig. 2a) and females (Fig. 2b). The incidence rates of most cancers rose with age until ages 85-94 years in men and women. However, lung carcinoma rates in men showed a decrease between ages 75-84 years.

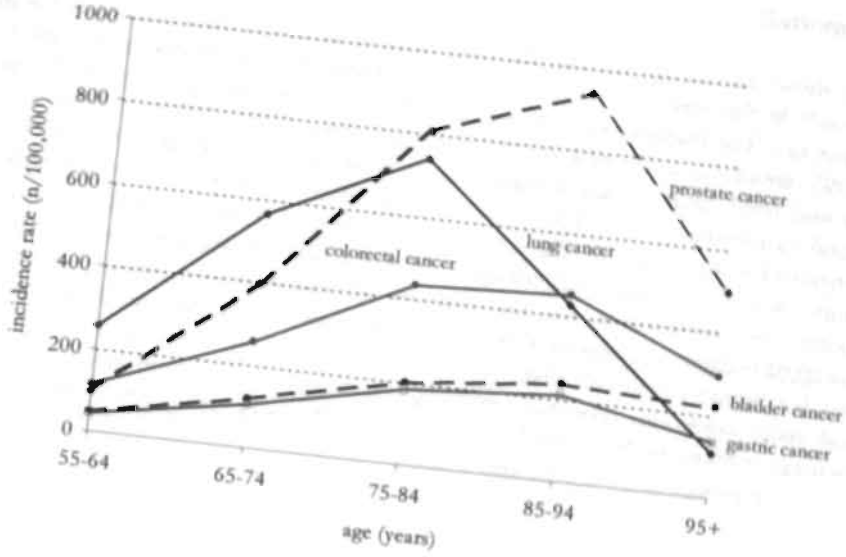

Figure 2a Annual age-specific incidence rates for common cancers in males; data derived from the Netherlands Cancer Registry, 1989-1995

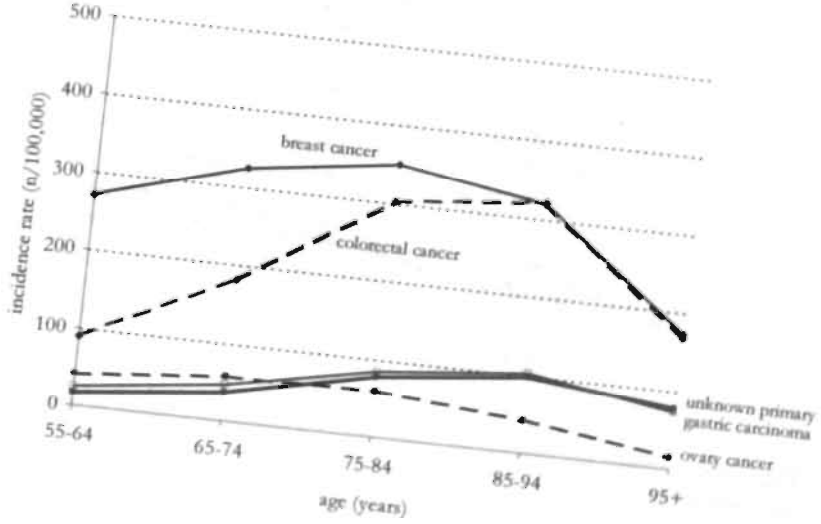

Figure 2b Annual age-specific incidence rates for common cancers in females; data derived from the Netherlands Cancer Registry, 1989-1995

Cancer mortality

Figure 1 shows annual age-specific mortality rates of all cancer sites combined for ma and females in the years 1991-1995. In both men and women, mortality increased w increasing age. The majority of cancer-related deaths in men age 95+ years in the peri 1991-1995 could be attributed to prostate carcinoma (1510/100,000) (Fig. 3a). T second and third most common malignancies were lung carcinoma (406/100,000) a colorectal carincoma (483/100,000). In men age 85-94 years, prostate carcinoma aga was responsible for most of the cancer-related deaths (1060/100,000), whereas lun carcinoma was the second most common (824/100,000). In the other age groups, lun carcinoma was responsible for the majority of cancer-related deaths, followed b colorectal or prostate carcinoma. Cancer death rates in women were, in all age categories highest for breast carcinoma (Fig. 3b). Until the age of 65 years, lung carcinoma was second most common, whereas colorectal carcinoma was second most common in women age $\geq$ 65 years. Mortality from an unknown primary tumor was more common in the older age groups in both men and women.

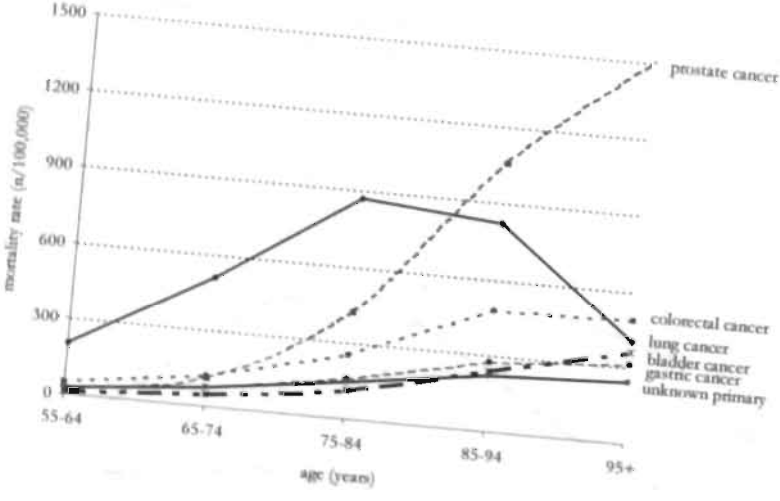

Figure 3a Annual age-specific mortality rates for common cancers in males; data derived from Statistics Netherlands, 1991-1995

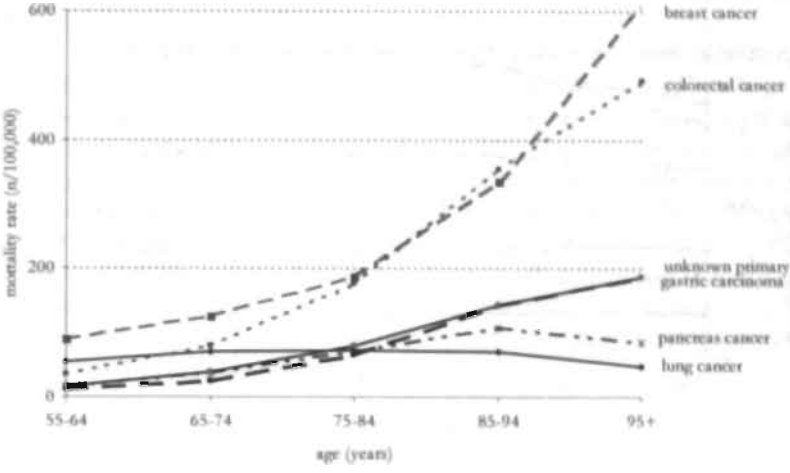

Figure 3b Annual age-specific mortality rates for common cancers in females
Data derived from Statistics Netherlands, 1991-1995

Trends in age-specific cancer mortality rates from 1976-1995 (5-year periods) are presented in Figure 4 (4a: males; 4b: females). Cancer mortality rates in males decreased or were stable below age 85 years, but increased by approximately 20% in persons ages 85-94 years and by 50% in persons age 95⁺ years. Female mortality rates were stable or decreased slightly, except in the 95⁺ years age group, in which the rates showed an increase in mortality until 1990 and then declined. Trends in age-specific rates of individual cancer sites (Fig. 5a-i) showed that for several common cancer sites, mortality rates were stable or decreased in the younger age groups, whereas they increased in the oldest age groups. In men this was noted for prostate carcinoma (Fig. 5a) and lung carcinoma (Fig. 5c), but not for colorectal carcinoma (Fig. 5b). In women this phenomenon was noted for breast carcinoma (Fig. 5f) and ovarian carcinoma (Fig. 5g), whereas for colorectal carcinoma (Fig. 5h) an increasing trend only was found in the age 95⁺ years group.

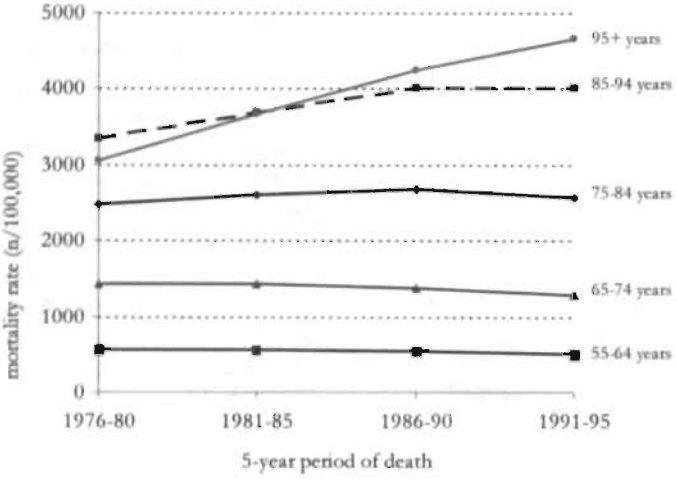

Figure 4a Trends in age-specific cancer mortality in males; data derived from Statistics Netherlands, 1976-1995

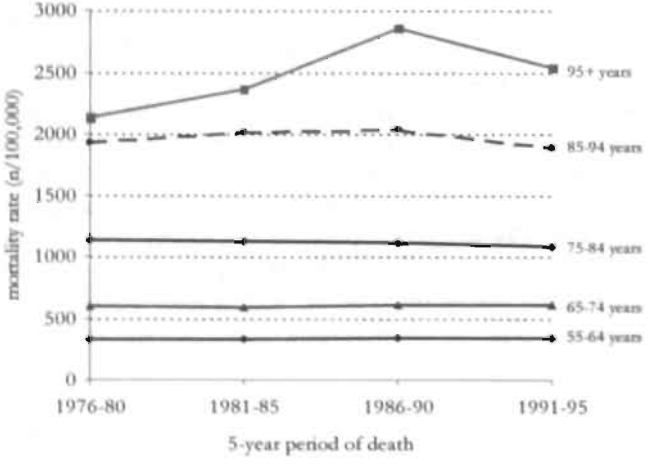

Figure 4b Trends in age-specific cancer mortality in females; data derived from Statistics Netherlands, 1976-1995

For unknown primary tumors, an increasing trend in mortality rates was found in men (Fig. 5d) and women (Fig. 5i) in all age groups, with the largest increase in the age groups 85-94 years and 95+ years. In contrast, in all age groups, gastric carcinoma mortality rates in men declined over the period 1975-1995 and declined most profoundly in the oldest age groups (Fig. 5e).

Proportionally, cancer as a cause of death became less prominent with increasing age, as shown in Figure 6. In the years 1991-1995, 42% of deaths in the total male population ages 55-64 years were attributed to cancer, whereas this applied to 52% of deaths in women; these proportions in men and women were 11% and 7%, respectively, in the 95+ years group. Approximately 40% of the very elderly died from cardiovascular diseases, whereas pneumonia also was a common cause of death with proportions comparable to those of cancer in the group of patients age 95+ years. In approximately 10% of the very elderly, the cause of death remained unknown because of incomplete description of the symptoms or disease. Over time (1976-1980 until 1990-1995) cancer as a cause of death in proportion to all causes of death increased in all age categories, varying between 6% in men ages 55-64 years to 0.3% in women age 95+ years.

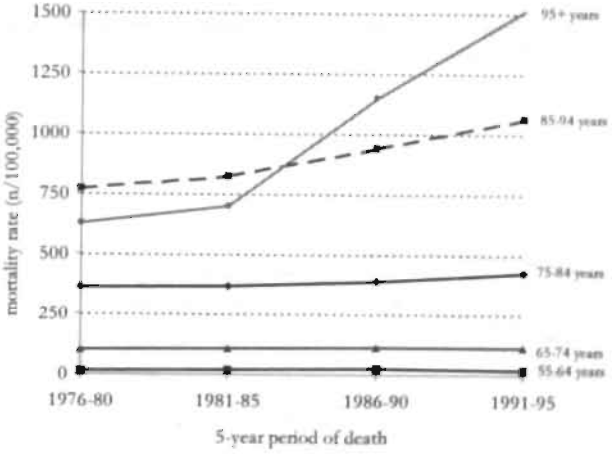

Figure 5a Trends in age-specific mortality rates for prostate carcinoma; data derived from Statistics Netherlands, 1976-1995

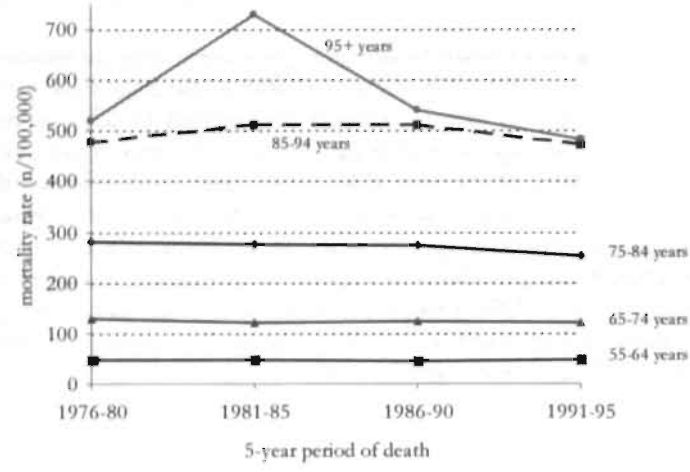

Figure 5b Trends in age-specific mortality rates for colorectal carcinoma in males; data derived from Statistics Netherlands, 1976-1995

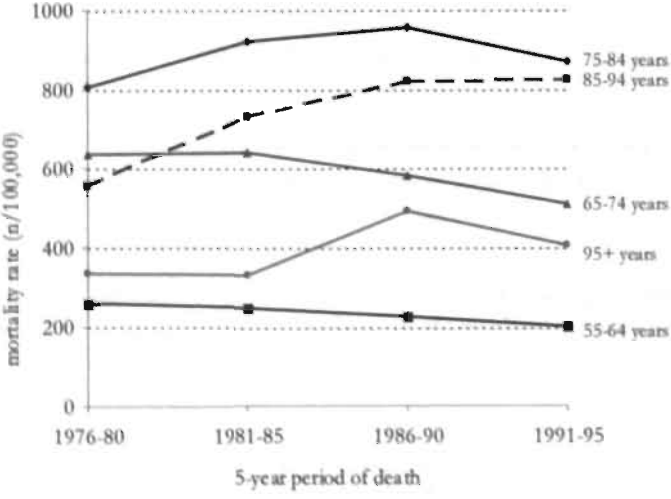

Figure 5c Trends in age-specific mortality rates for lung carcinoma in males; data derived from Statistics Netherlands, 1976-1995

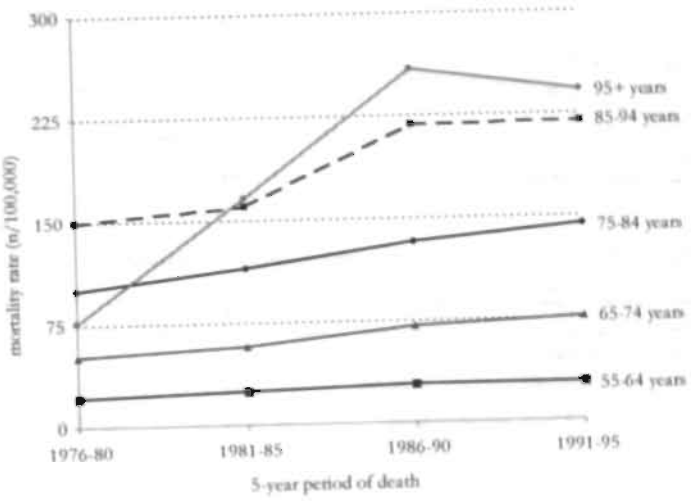

Figure 5d Trends in age-specific mortality rates for unknown primary tumours in males; data derived from Statistics Netherlands, 1976-1995

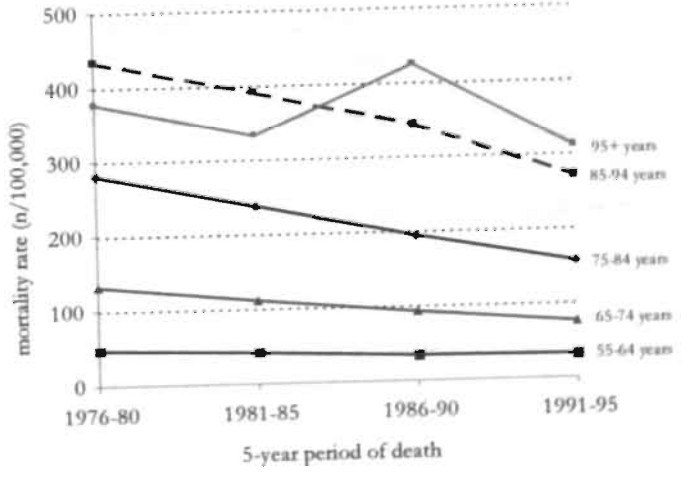

Figure 5e Trends in age-specific mortality rates for gastric carcinoma in males; data derived from Statistics Netherlands, 1976-1995

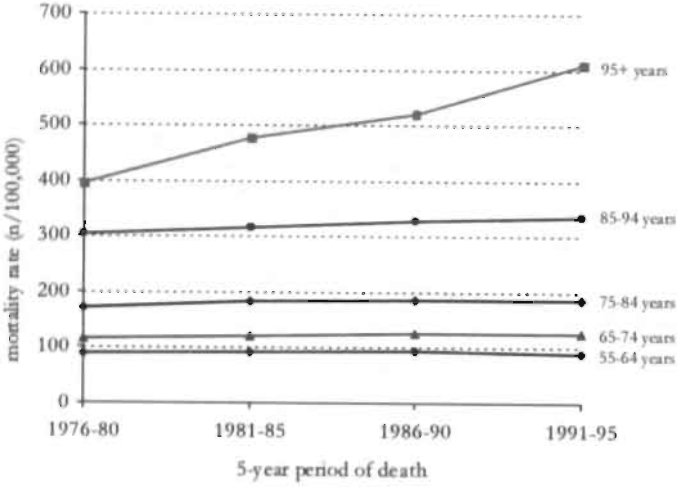

Figure 5f Trends in age-specific mortality rates for breast carcinoma in females; data derived from Statistics Netherlands, 1976-1995

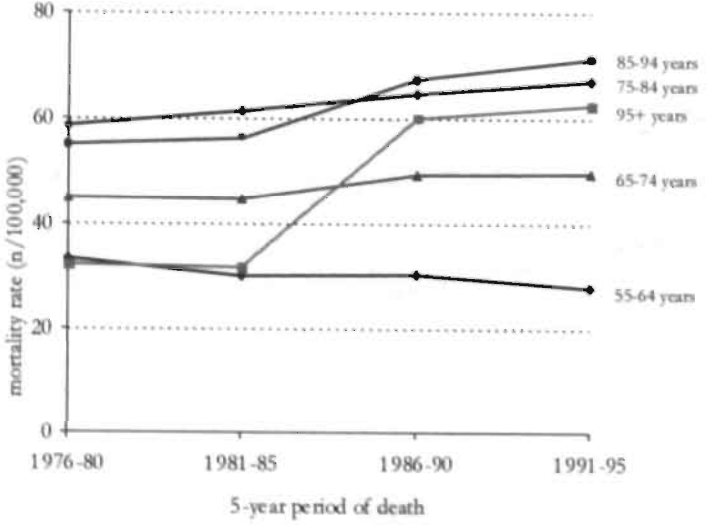

Figure 5g Trends in age-specific mortality rates for ovarian carcinoma; data derived from Statistics Netherlands, 1976-1995

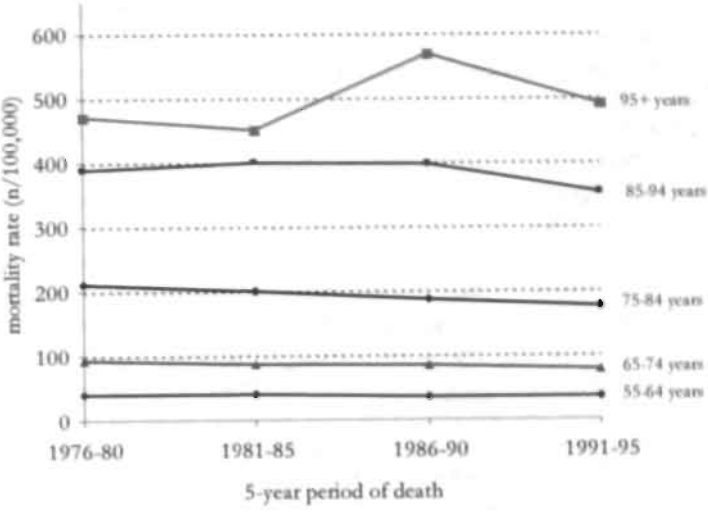

Figure 5h Trends in age-specific mortality rates for colorectal carcinoma in females; data derived from Statistics Netherlands, 1976-1995

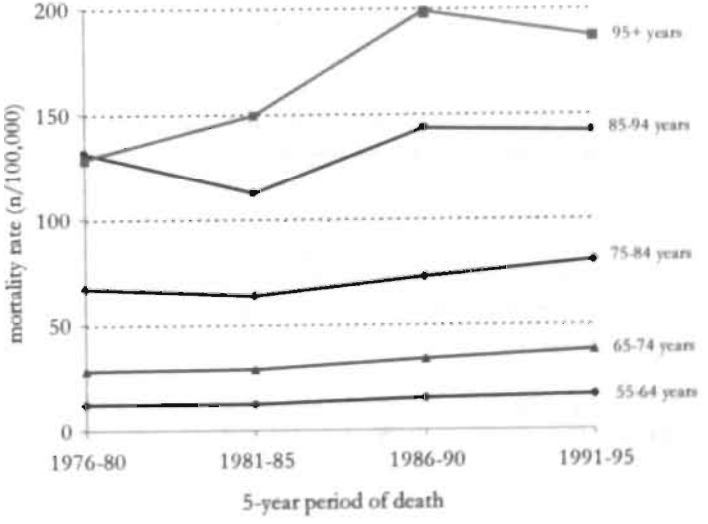

Figure 5i Trends in age-specific mortality rates for unknown primary tumours in females; data derived from Statistics Netherlands, 1976-1995

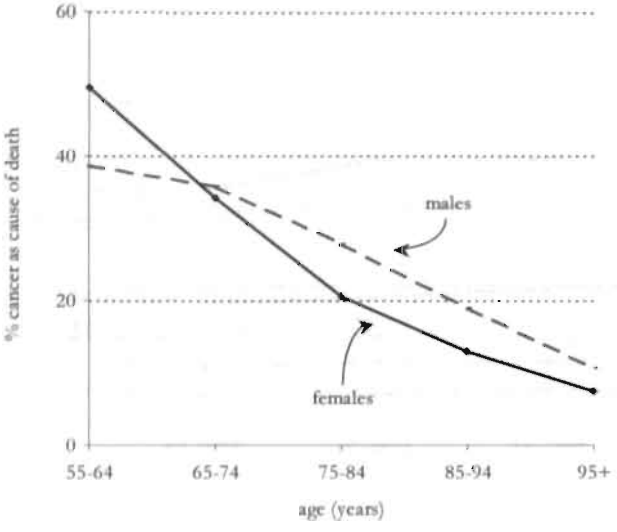

Figure 6 Percentage of deaths by age category that were attributed to cancer in males and females; data derived from Statistics Netherlands, 1976-1995

Discussion

Age-specific Incidence Rate

Despite a clear proportional decrease with increasing age, cancer in the very elderly population in the Netherlands (age 85+ years) appears to be an important cause of morbidity, with peak incidence rates for most common sites. In the period 1989-1995, cancer was diagnosed annually in nearly 3% of Dutch men age $\geq$ 85 years and in nearly 1.5% of very elderly Dutch women. The pattern of age-specific incidence rates of all cancers combined showed an increase with increasing age until ages 85-94 years, whereafter it declined. This applied to most of the common cancers in men and in women, except for lung carcinoma in men in which incidence rates have started to decrease in patients ages 75-84 years.

In a study conducted during the period 1988-1993 in California (USA)[8] colorectal carcinoma was most common in women age 90+ years, with breast carcinoma the second most common malignancy. Skin cancer was not included in the analyses. In the current study, breast carcinoma was the most common malignancy in women ages 55-84 years, whereas colorectal carcinoma was the most common malingnancy in the group of patients ages 85-94 years; the difference between the number of patients with colorectal carcinoma and breast carcinoma was very small (10 cases). In both series, prostate carcinoma was the most common in the very elderly men, followed by colorectal carcinoma, whereas lung carcinoma was most common in men ages 55-75 years.

Aging and cancer

Various theories exist to explain the age-dependent increase in cancer incidence rates. First, natural changes in the internal milieu of the organism (immune, endocrine, or metabolic) are believed to provide increasingly favorable conditions for the malignant transformation of cells with increasing age [9,10]. Second, the age-related accumulation of carcinogens might account for epithelial carcinoma induction as a function of age in sensitive individuals [11]. Third, decreased ability to repair DNA damage in older cells may influence the process of neoplastic transformation [12]. Fourth, oncogenic activation or amplification might be increased in the older host, resulting in the increased initiation or promotion or differential clonal evolution [13]. Fifth, a decrease in immune surveillance, or immunosenescence, might contribute to the increased incidence rate [13]. These concepts were formulated mainly on the basis of studies showing sharp increases in incidence rate with increasing age in persons ages 75+ years or 85+ years when considered as a single category. However, we found that above the age of 85 years the incidence rates of the most common cancers decreased. Without paying further attention to the *pros and cons* of these theories, they all expect the rise in incidence rates to continue with age, also above the age of 85 years, as we found for mortality rates.

Can the underreporting of cancer in the very elderly, because of less extensive diagnostic workups, explain the deficit?[14] In the current study population the percentage of patients with histologically or cytologically confirmed diagnoses varied with age in males as well as in females. In the age group 55-64 years these percentages were 98% in males and 97% in females, whereas in patients $\geq$ 95 years these rates were 87% and 84%, respectively.

Could this generation, born at the beginning of the 20th century, have been less prone to risk factors or had exposure to other risk factors than the younger generations? For instance, changing smoking patterns have affected the incidence rate of lung carcinoma between different birth cohorts (cohort effect). It has been suggested that natural selection allows the less cancer-prone population to survive [13,15]. Genetic resistance against the many steps in pathogenesis may be accumulated over time. However, if the latter were true, we would have expected to find decreasing mortality rates, as Smith reported [15].

Age-specific Mortality Rates

Mortality rates for common cancers in adulthood mostly were observed to increase throughout the latter part of the life span, except for carcinomas of the lung and pancreas in both genders and ovarian carcinoma in women, which declined in the very elderly age groups.

To our knowledge there are very few published mortality data regarding cancer patients beyond age $\geq$ 85 years. Hadley [16] described an increase in age-specific mortality rates from all cancers combined and from most individual cancers, except for lung carcinoma. However, Smith [15] studied cancer mortality in very elderly people in the U.S. in 1990 and found decreasing mortality rates at age 90-94 years and ages 95-99 years for the major cancer sites, except for breast carcinoma in women, which showed an increasing mortality rate in women age > 100 years. At the current time, we are not able to provide a plausible explanation for these different findings.

Mortality Trends

A clear increase in age-specific cancer mortality rates was observed in very elderly men over the period 1976-1995, whereas in the younger age groups mortality rates declined. The increase in mortality in men can be attributed largely to an increase in prostate carcinoma and lung carcinoma deaths. In women age 95^{+} years there was an increase in mortality until 1990, which could be attributed largely to a rise in breast and ovarian carcinomas. In both men and women, deaths from unknown primary tumors contributed to the rise in mortality to a smaller extent.

Similar patterns of breast and ovarian carcinomas, comprising declining or stable mortality rates in younger age patients and increasing rates in older age patients, have been described previously [17-20], also in the Netherlands [21,22]. No upward trend in cancer mortality was found in a worldwide study on cancer mortality in the elderly (65-84 years) [23]. In fact, the pattern in elderly women was very favorable, because the lung cancer carcinoma epidemic still was in its early phases in most countries and there were downward trends in gastric carcinoma and gynecologic carcinoma mortality, which are particularly relevant. Researchers in Japan reported a rapid rise in cancer mortality in their very elderly male population (1950-1990)[24]. The authors suggested that a real increase in cancer mortality may have occurred, although a tendency to perform more thorough diagnostic workups in the very elderly also may have contributed to the increase.

Explanations for Mortality Trends

Several phenomena might be responsible for the gradual increase in cancer mortality in the very elderly. As mortality from cardiovascular diseases has decreased over the past few decades (in the Netherlands from 416 in 1970 to 350 per 100,000 males in 1990) [25], the probability of dying from other causes (e.g., cancer) has increased (competing causes). The decrease in incidence rate of male lung carincoma (since 1980) and gastric carcinoma (since 1950) may have had a similar effect. Part of the increase in prostate carcinoma mortality may be the result of an increase in exposure to risk factors, because major causes of prostate carcinoma still are unknown.

Several factors have been put forward to explain the increase in ovarian and breast carcinoma in very elderly women. Changes in parity (decreasing number of live births since the beginning of this century) between different birth cohorts of women could explain some of the variation [17,20]. The widespread use of oral contraceptives also has been suggested to be a contributing factor in the decline in ovarian carcinoma mortality rates in the younger age groups [20]. Improvement in treatment outcomes in general without "real cure" (delayed mortality) and earlier diagnosis and more effective early treatment in the young are other possible causes that have been put forward [16,21,26,27]. The completeness and reliability of recorded data also may affect trends over time, especially in the very elderly [26,29]. For example, a study in Hiroshima compared the diagnosis recorded on death certificates with those recorded at autopsy over a 28-year period [29]. Inaccuracy of death certificate diagnoses was greatest in the elderly, but there was improvement in accuracy for many cancer sites over time. Similar circumstances may explain in part the increase in mortality rates found in the current study.

We conclude that the highest incidence rates of major cancers were observed in the very elderly population in the Netherlands. Age-specific mortality rates increased with age. During the period 1976-1995 there was a rising trend in cancer mortality in the very elderly. This was partly real and partly artifactual. Based on high incidence rates, cancer mainly appears to affect the elderly. However, proportionally, < 10% of the very elderly die from cancer.

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7 General Discussion

Main findings

In this thesis, age-specific differences in diagnostics, treatment and survival were studied for some common malignancies. It appeared that a substantial proportion of elderly patients did not profit optimally from the available curative and palliative treatment modalities. We found fewer diagnostic and staging procedures in the elderly and significant differences in treatment between elderly and younger cancer patients. Elderly cancer patients were more likely to receive no treatment or less intensive treatment. Particularly large differences were found in treatment for lung cancer patients by age, with high proportions of untreated patients among the elderly. Factors such as more comorbidity or a low performance status could not sufficiently explain these differences. In patients with epithelial ovarian cancer, differences in treatment and survival were found. In cervical cancer patients, survival differences by age were less clear. The study on cancer incidence and cancer mortality among the very elderly population of the Netherlands showed peak incidence rates for most common sites; incidence rates increased with increasing age until the age of 85-94 years, whereafter they declined. Mortality rates for common types of cancer increased throughout the latter part of the life span, except for carcinoma of the lung, pancreas and ovary, which declined in the very elderly age groups.

Methodological issues

Data collection

Most of the data analysed in this thesis were provided by the Regional Cancer Registry Maastricht, kept by the Comprehensive Cancer Centre Limburg (IKL). In order to increase the power in two studies (Chapters 3 and 4) we received co-operation from the cancer registries kept by the Comprehensive Cancer Centre South (IKZ) and the Comprehensive Cancer Centre East (IKO). In the study on cancer in the very elderly, data on the complete Dutch population were provided by the Netherlands Cancer Registry (NCR) and Statistics Netherlands (Ch. 6).

In the two studies in which age-specific survival was addressed, we required information on the vital status of the patients. Unfortunately, in the Netherlands, it is still a problem in terms of time, money and privacy, to obtain complete follow-up data on cancer patients for survival studies. Several sources need to be consulted, such as medical files, municipal population registries, and the Bureau for Genealogy (CBG), the nation-wide registry of deceased Dutch citizens. Currently, attempts are being made to set up a regular link with the national system of municipal population registries. When this has been realised, it will be possible to calculate survival rates on a regular basis, in the same way as incidence and mortality rates.

In an international context, cancer registries in the Netherlands collect a fairly extensive data set, including clinical stage, pathological stage and initial treatment. Data on e.g. the dose of cytotoxic drugs administered, the number of treatment cycles, or the dose of radiotherapy and whether the treatment was stopped prematurely, are not included.

However, these are all items that may be relevant to the age-specific differences found in the first study (Ch. 2) and in the two gynaecological studies (Chapters 3 and 4). Also, no information is recorded about comorbidity or performance status. These factors may help to explain why a patient did not receive treatment or less intensive treatment. Therefore, in the lung cancer study (Ch. 5) registration clerks collected additional information on comorbidity, performance status, treatment details and pulmonary function.

Quality of the data

Validity and completeness

A very important characteristic of the cancer registry system in the Netherlands is the very high quality of the data. Data from the registries of the IKL and IKZ have been included in the leading publication 'Cancer incidence in five continents' since 1992 [1-3]. Furthermore, several studies have been carried out which revealed high validity and completeness of case ascertainment, also in the oldest age groups [4,5]. Above the age of 80 years, completeness was still 97%. Validity is defined in this thesis as the proportion of cases in the registry with a given characteristic (e.g. cancer site, or age] that truly do have the characteristic [6]. Completeness is defined as the degree to which all relevant cases are recorded. Also important is the completeness of the data in terms of missing information (the cases for which particular variables are unknown)[6]. Results might be biased when certain groups, e.g. age groups, have higher proportions of missing information on specific items. In the studies presented in this thesis, the most striking item with high unknown information proportions was stage at diagnosis in the elderly. Furthermore, patients with stage unknown often also had other variables missing, such as treatment (Ch. 2], comorbidity and performance status (Ch. 5]. As stage unknown occurred more often in the elderly than in the younger patients, the proportion of elderly patients for whom patterns of care could be described was somewhat limited. In the population-based studies in this thesis, however, it was exactly their purpose to gain insight into the current situation and draw attention to this unsatisfactory situation.

Comorbidity and performance status

To record comorbidity, methods introduced by the adjacent cancer registry kept by the IKZ were used. This registry started to record comorbidity in 1993 and has also carried out a validation study [7]. Comorbidity is recorded by means of an adapted version of the Charlson Comorbidity Index [8], which is well-defined and validated. Since 1999 comorbidity has formed part of the standard registration item of the IKL for some common malignancies (lung, oesophagus, head/neck, ovary and cervix].

Registration of performance status, which is an important prognostic factor especially for lung cancer patients [9], is much more complicated. Performance status as such is not well-documented and often missing from the medical files, except in patients treated in a trial setting or at a radiotherapy department. Therefore, the registration clerks were instructed to make notes on the condition of the patient based on the medical and nursing reports. Then from those notes, a performance status was derived according to the WHO scale which was first described by Zubrod et al [10]. The idea to do it this way stemmed from a study of Greenfield, who used nursing notes to define the performance status of cancer patients [11].

Unfortunately, even after much effort, no performance status could be derived from the medical files in 24% of the cases, with comparable proportions among all the age-groups. In order not to lose information on too many patients, performance status unknown was also included in the data analyses.
Treatment choice could not be explained by performance status, which is in agreement with others [12]. However, comparison between studies may be difficult. Although scales for performance status are well-validated (WHO, Zubrod, Karnofsky] it is not known whether the method of collection is uniformly reliable. Furthermore it has been stated that the application of the WHO score or the Karnofsky score to older cancer patients can be problematic, because the degree of functional impairment may be underreported. More precisely: 80% of the older patients scored 0 or 1 although more than 90% had comorbidities and less than half were independent in ADL (activities of daily life) [13]. Therefore, the use of an ADL scale would probably had been more accurate and informative. At present, it is quite impossible to retrieve this information retrospectively from medical files.

The effect of treatment differences on survival

Two studies in this thesis, addressed age-specific differences in survival (Chapters 3 and 4). In patients with epithelial ovarian cancer, age-specific differences in survival remained valid even within the group of patients who had undergone surgery and chemotherapy, which was the standard treatment for this type of cancer in that period. In contrast with these findings, it was found that in a subgroup of cervical cancer patients, age was not an independent factor after adjustment had been made for treatment. In both studies, the effect of treatment on survival was considered to be the result of patient selection on prognostic characteristics within the treatment groups, such as tumour volume (a larger tumour meant a poorer prognosis), comorbidity and performance status. This view was based on the fact that in observational studies it is very difficult to estimate any real differences in outcome between groups that received different treatment. This is because the above-mentioned prognostic factors were not equally distributed over the groups [14], and proper adjustment for these factors was not always possible due to a lack of detailed documentation. For example, in the ovarian cancer patients treated with surgery and chemotherapy, no information was available about the presence of residual disease after surgery or about dosage reduction of chemotherapy. It is not so that only randomised studies can provide reliable evaluations of treatment interventions [15]. According to McKee et al, randomised and non-randomised studies can provide complementary evidence when prognostic factors are well understood, measured and controlled for. It is important that clinicians who use this evidence are aware of the strengths and weaknesses of each method.

Treatment options for elderly cancer patients

Surgery

The studies in this thesis revealed reluctance to operate on elderly patients with locoregional non-small cell lung cancer, breast cancer, advanced ovarian cancer and cervical cancer. Surgery is still the main treatment modality for most solid tumours. However, what constitutes 'adequate' or 'appropriate' surgical therapy for the elderly is not always accurately known [16]. We do not know whether it should be any different from the standard treatment provided to younger patients, because very few scientific data on the older population are available from randomised trials. In the past, surgery has been viewed to carry prohibitive risks for many elderly patients, but many recent studies have indicated that surgical procedures can be performed safely in the elderly [16-18]. Apparently, careful preoperative assessment of the patient is of the main importance; increased morbidity and mortality from surgery are associated with advanced stage disease and emergency procedures [16]. Older patients are more likely to be diagnosed with more advanced stage disease, which was confirmed by the studies in this thesis. Therefore, early diagnosis and treatment in the elderly should be encouraged.

Radiotherapy

Radiotherapy plays an important role in the management of elderly cancer patients. The majority of elderly patients with locoregional non-small cell lung cancer received radiotherapy with curative intent (Ch. 5). This was also the case for elderly patients with cervical cancer stage IB-IIA (Ch. 4). In patients with non-Hodgkin lymphoma stage I, the percentage of patients treated with radiotherapy also increased with increasing age. Proportions of patients with advanced NSCLC that received radiotherapy for palliation decreased with increasing age.

Radiotherapy is of particular benefit to older and frail cancer patients as an alternative to surgery and systemic therapy. Existing data on the use of radiotherapy in elderly patients indicate that this treatment modality can be applied to older people without increased toxicity [19,20]. Also, some investigators reported on the tolerance of cancer patients over the age of 80 years to radiotherapy and the outcome [21]. Side-effects were comparable with those observed in younger patients. Oguchi et al [22] even recommended radiotherapy when applicable for patients aged over 90 years. However, the patients in most of the studies had good performance status with little functional impairment and were not representative of the general older population. A clear disadvantage of radiotherapy especially for the older population is the long duration of therapy (about 6-7 weeks for curative treatment and 2-4 weeks for palliative treatment) [21]. An American study found that use of radiotherapy varied with the distance from the patient's home to the radiotherapy department [23]. Distances in the US, however, are not comparable with those in the Netherlands. In a study on breast cancer patients in the Netherlands (IKZ), the distance to the radiotherapy department per se was not found to affect the use of radiotherapy [24]. In frail elderly patients with cancer, radiotherapy is the most widely used treatment modality [21].

Chemotherapy and endocrine therapy

Compared to radiotherapy, the role of chemotherapy in the management of elderly cancer patients was found to be small. The first study in this thesis (Ch. 2) showed that patients aged over 70 years with ovarian or colorectal cancer or NHLwere less likely to receive (adjuvant) chemotherapy.
Important studies have shown that age itself is not an absolute contraindication to cytotoxic chemotherapy [25, 26]. However, these studies are not considered to be representative of the whole geriatric population, because older individuals were under-represented, especially the very elderly (85^+ years). In addition, patients were selected on the basis of an absence of severe comorbidity and good performance status. Furthermore, many of the chemotherapy regimens used in these studies had lower dose intensity than regimens in current use. Lymphoma studies that were specifically directed at older patients presented different findings: firstly, older individuals seemed to be at increased risk for myelotoxicity, the most common complication of chemotherapy. Secondly, haemopoietic growth factors were found to be effective in older individuals and thus enabled the administration of chemotherapy at full dosages. Studies on the treatment of elderly patients with NHL have also been performed in the catchment area of the IKL [27,28]. It was found that 26 out of 68 NHL patients aged 60 years and older were not treated optimally (anthracycline containing chemotherapy, CHOP/CNOP) and that in 9 of them the reason was advanced age, despite good performance status [27]. Subsequently, attention was paid to the problem of elderly patients by physicians, and regional protocols were designed in which the use of growth factor G-CSF in addition to CHOP was advocated. This resulted in more elderly patients being treated with the standard chemotherapy regimens, without any major set-backs and with favourable outcomes [28].

It is well-recognised that endocrine therapy plays an important role in breast cancer patients especially in the elderly, because their tumours are often hormone responsive. Tamoxifen is the most widely used endocrine therapy today and it also has the advantage of virtually no-side effects [29]. This is reflected in the results described in Ch. 2: patients of over 70 years with locally advanced breast cancer were more likely to receive adjuvant endocrine therapy than adjuvant radiotherapy.

Cancer survival in the elderly

Poorer survival rates were observed in this thesis for elderly ovarian cancer patients and for elderly cervical cancer patients with advanced stage. These results are in agreement with other population-based studies, confirming a poorer prognosis for elderly patients [30-33]. In the lung cancer study in this thesis (Ch. 5) it was not possible to carry out a survival analysis, because of incomplete follow up. Van Dijck et al. however, affiliated to the cancer registry kept by the IKO, studied treatment and survival in patients with non-small cell lung cancer stage IIIA (n=212) diagnosed in 1989-1994 [34]. It was found that the prognosis was poorer in patients who were older than 74 years, had at least one comorbid disease, had not received treatment or who had lymph node metastases.

The Eurocare II project is paying particular attention to survival in the elderly, in order to increase awareness of the need to develop better prevention and clinical management strategies [35]. Survival data on 701521 elderly European patients aged between 65 and 99 years and diagnosed between 1985 and 1989 were analysed. It was found that survival was poorer in the elderly patients than in those aged between 55 and 64 years for every site (stomach, colon, rectum, pancreas, lung, larynx, melanoma, breast, ovary, uterine cervix, uterine corpus, prostate, bladder, kidney, thyroid, NHL). It was also found that differences between older women and younger women were larger than those between older men and younger men. However, one must bear in mind that correction for stage was not possible in these analyses, because Eurocare does not have this information.
Age-related differences in survival in general are considered to stem from different factors, including different diagnostic approaches and treatment of elderly cancer patients; this is discussed in the next paragraph. It has also been argued that age-specific differences in the biological behaviour of some tumours may be associated with a poorer prognosis in older patients. This has been demonstrated for example in patients with acute myelogenous leukaemia (AML), large cell non-Hodgkin lymphoma (NHL) and some forms of cancer of the ovary. In contrast, breast cancer and non-small cell lung cancer did show a more indolent disease in the majority of the elderly patients [36]. Existing evidence for differences in tumour behaviour with age is, however, still limited and controversial [37].

Factors that influence the choice of treatment in elderly cancer patients

The studies described in chapters 2 to 4 showed that the degree and nature of the age-related differences in treatment varied according to tumour localisation. For example, large age-specific differences were found in patients with lung cancer, while fairly small differences were found in patients with colorectal cancer. The results of the lung cancer study showed that even after adjusting for comorbidity and performance status, age was an independent factor for not receiving treatment according to the guidelines (Ch. 5). This strongly suggests that in lung cancer, calendar age forms the greatest argument to deviate from standard treatment protocols. The question arises as to whether this is a typical finding in lung cancer patients and whether other factors strengthen or weaken the influence of calendar age. Other authors identified and categorised factors that influence the management of elderly cancer patients: a) patient-related factors and b) physician or care provider-related factors [36,38]. Examples of patient-related factors are physical and mental status, age, social support and a patient's own preferences. Examples of care provider-related factors are communication skills, care policies and preferences. Findings in the studies in this thesis indicate that another category should be added: c) tumour-related factors, including prognosis (type and stage of the tumour), treatment opportunities and risks. In Table 1 all these factors are summarized, while the following paragraphs highlight some of the factors that strengthen or affect the influence of calendar age separately or in combination, and are most relevant to the results described in this thesis.

Table 1 Factors that influence the choice of treatment in elderly cancer patients

Patient-related	• physical and mental status – comorbidity – performance/functional status – nutritional level • environment/background – social network/family – educational level – financial situation • patient's preferences, beliefs, ignorance • calendar age
Physician/care provider-related	• knowledge/experience • attitude/communication skills • hospital policies • care provider's preferences • availability of care
Tumour-related	• prognosis – type of tumour – stage • treatment opportunities – risks of treatment – risks of withholding treatment

The prognosis (tumour-related)

Firstly, it seems that physicians are most likely to deviate from the standard treatment protocol if they have little hope that the treatment will be effective. Patients with lung cancer have a very poor prognosis. Survival in patients with non-small cell lung carcinoma in the Netherlands is only 15% [39]. Recent improvements in survival by means of e.g. chemotherapy are in the order of 4-6 weeks. Both patients and physicians hold pessimistic views about the effectiveness of treatment and palliation. The reputation that chemotherapy involves severe and highly unpleasant side-effects still alarms many patients. It is likely that this nihilism regarding treatment will be less intense when the results achieved by treatment are more promising. For example, the study on cervical cancer (Ch. 4) showed that the majority of patients, including elderly patients, received standard treatment. However, in contrast with lung cancer, the overall prognosis of cervical cancer was far better: 67% of the patients were still alive after 5 years.

Nature and risks of treatment (tumour-related)

Secondly, it is conceivable that the decision of whether or not to apply standard treatment to an elderly patient might depend on the nature and complexity of treatment. For certain forms of cancer, e.g. breast cancer, there is a wide diversity of treatment combinations. Several studies on breast cancer have shown that elderly patients receive less extensive treatment or are treated less adequately than younger patients [24,40]. We confirmed these findings in our first study: 14% of the elderly patients with stage I-III breast cancer and 59% of the elderly patients with stage IV received endocrine therapy alone.

This single modality treatment was applied despite the fact that it has been known since the late nineteen eighties that Tamoxifen alone does not constitute adequate treatment in early stage breast cancer [41,42]. It is possible that physicians are extra cautious in the case of elderly patients, because they are worried that certain forms of treatment might be too drastic for them. This may also apply to patients with ovarian cancer who receive extensive abdominal surgery (debulking) that is essential to the further course of disease. In a study on patients with stage III-IV ovarian cancer, Gershenson [43] found that more elderly women had bulky residual disease after primary debulking, possibly because the primary debulking operation had been less aggressive. Although post-operative chemotherapy is standard policy for ovarian cancer stages III-IV, in our study only 37% of patients aged 70 years and older received this treatment combination, compared to 71% of the patients of younger than 55 years and 54% of the patients aged 55-69 years. One of the reasons may be that chemotherapeutic treatments for cancer patients are still associated with significant toxicity. Currently, studies on chemotherapy regimens for older patients are being performed to gain more insight into toxicity, survival and response rates in the elderly.

Risks of withholding treatment (tumour-related)

Risks of withholding a certain form of treatment might also play a role in decision-making. For example, in the case of colorectal cancer, there is only one treatment: surgery. In a study on 670 patients with colorectal cancer, Guagdagnoli did not find any differences in treatment between the various age categories [44]. Damhuis looked specifically at resection rates in patients with lung, stomach and colorectal cancer; differences per age category were smallest for colorectal cancer [45]. Thus, despite the fairly large operation risk (1-10%), surgery for colorectal cancer is still considered to be justified even in elderly patients, possibly because if surgery is withheld, there is a considerable risk of intestinal obstruction. In the study described in chapter 2 it was found that differences between age categories were marginal for this form of cancer. In contrast, surgery was performed less often in elderly patients with lung cancer, despite the tumour being operable. However, in the case of lung cancer, radiotherapy is considered to be a good alternative for patients whose tumour is smaller than 4 cm in size [46].

Health care system / availability of care (care provider-related)

A fourth factor that might be of importance in the decision of whether or not to apply standard treatment to elderly patients, lies on the side of the care providers. For example, a Scottish population-based study on 1423 (early stage) lung cancer patients showed that being referred to a lung specialist or being treated by a lung specialist had a significant influence on the chance of receiving treatment with curative intent [47].

In the Netherlands, patients with head and neck cancer are treated centrally at university hospitals. Treatments are protocolised and applied by a team of specialised health professionals. It appeared that there were hardly any age-specific differences in treatment in these patients (see Ch. 2). This is worthy of note in view of the high prevalence of comorbidities among patients with these alcohol and smoking-related forms of cancer [7].

Characteristics of the hospitals themselves (e.g. size, teaching hospital, treatment policies) might also affect decisions. In a population-based study using data from the Comprehensive Cancer Centre South (IKZ), Post et al found substantial variation in treatment for prostate cancer patients. More than twice as many patients diagnosed at larger hospitals underwent radical prostatectomy than those diagnosed at smaller hospitals [48].

In a population-based study by the Comprehensive Cancer Centre East (IKO) on non-small cell lung cancer patients stage IIIA, differences in resection rates were revealed between six participating hospitals [34].
One of the main characteristics of ageing is the growing distinction between individuals, physical and also social status, psychological and functional status. These factors determine the biological age of a person and it is obvious that calendar age alone is not a valid criterion for the choice of cancer treatment. Calendar age may be a starting-point for decision-making regarding how to treat a particular patient, while successively taking into account all other relevant factors. Only then can the decision to withhold or adapt treatment be justified.

Geriatric assessment of elderly cancer patients

When deciding on the optimal treatment for elderly cancer patients, it has been internationally recognised that the best guide can probably be obtained by making a comprehensive multidimensional assessment of the patient. This assessment should evaluate areas such as comorbidity, performance/functional status, emotional and cognitive conditions, socio-economic conditions, nutrition and use of medication. It is well-known that the number and seriousness of comorbid conditions, the degree of functional dependence, cognitive deterioration and the presence of depression are related to life-expectancy [13].

A comprehensive geriatric assessment with follow-up has proven useful in several geriatric studies [49,50] and is considered as being useful in cancer patients for at least four purposes [13,36]:

1. to estimate a patient's life-expectancy;
2. to identify frail individuals who are at excessive risk;
3. to identify problems that may prevent the standard administration of chemotherapy or radiotherapy (e.g. lack of social support or transportation);
4. to provide a common basis, i.e. a common language, in outcome research and quality assurance.

The problem with making such a comprehensive assessment is that it will be time-consuming and implementation will only be feasible at a few large cancer centres. Besides, not all patients can or should undergo an extensive geriatric assessment. Balducci et al recommended screening for all patients aged 70 years and older by means of a number of questions to determine who should or should not undergo more extensive examination before choosing (optimal) treatment [51]. Based on these recommendations, we composed a two-step assessment procedure (see Table 2). The first step comprises a physical examination and specific questions to detect problems in physical, cognitive and emotional functioning; the medical history provides information about the family situation, medication use and comorbidities. When a problem is suspected in one of these fields, step two consists of completing formal questionnaires to confirm or exclude the problem.

With the information derived from this two-step assessment, estimates can be made of the life-expectancy of a patient and of the tolerance and compliance to certain treatment modalities, which together form the foundation for the diagnostic approach and the therapeutic plan.

Table 2 Two-step geriatric assessment of patients aged 70 years and older

Parameter	Assessment tool	
	First step (screening)	Second step (confirmatory)
Physical functioning	• Physical examination • Set of 5 questions: – *Can you dress yourself?* – *Can you eat without help?* – *Do you need help taking a bath or a shower?* – *Do you drive?* – *Can you call somebody on the telephone?*	• Formal ADL (Activities for Daily Living) test (e.g. Barthel index [52] or Katz scale [53]) and IADL (Instrumental activities for Daily Living test (e.g. Lawton scale [54])
Cognitive/mental functioning	• Set of two questions: – *Can you repeat the three objects that will be mentioned (ask the patient to repeat them a few minutes later (three-item recall).* – *Can you tell me what day and year it is?*	• Mini-Mental Status Examination (Folstein, 1984 [55])
Emotional status	• One question: – *Do you often feel depressed or sad?*	• Geriatric Depression Scale [56, 57]
Comorbidity	• Document number and type of diseases	• Grade the seriousness (Charlson index [8])
Family situation/social support	• Medical history	• Discuss needs and solutions
Patient's opinion and preferences	• Medical history	
Medication use	• Review number and type of medication	• Look for duplications, interactions and compliance
Nutrition	• Calculate Body Mass Index, ask for weight loss	• Mini-Nutritional Assessment (Guigoz 1997 [58])

Recommendations and future research

Regular oncology practice

Calendar age is a major barrier against adequate cancer treatment for the elderly. However, to be able to evaluate the quality of treatment, particularly in relation with the heterogeneity of the patient group, detailed data are needed, in the same way that data are needed to adequately refer these patients for treatment. Assessments should not only include comorbidity and performance status, but also cognitive status, nutritional level and social and economic circumstances. The assessment tool described in the previous paragraph could be used for this purpose. Based on such an assessment, the benefits of treatment, e.g. prolonged survival, maintenance or improvement of quality of life and palliation of symptoms, can be weighed against the risks of treatment, such as toxicity of chemotherapy or complications after surgery.

Clinical research

It is of great importance to set up clinical research that does not exclude patients on the basis of calendar age, comorbidity or performance status [59]. Over the past few years, there has been an increase in trials that do not make age restrictions, or are specifically aimed at elderly patients. Important factors that initially formed reasons to exclude them from research (e.g. comorbidity and performance status) are now the very reasons why it is important to study elderly individuals specifically. In these trials, quality of life should also form an endpoint, because survival will not always be a suitable outcome variable owing to the lower life expectancy of elderly patients. The representation of older patients in clinical trials, however, is still very low [60], and often only relatively healthy patients are included. Recruiting elderly patients for clinical research will require special attention in view of the low general participation rate of patients in oncological studies [61,62].

Cancer registry

In many of the above-described facets of oncological care (registration, evaluation, trial participation), Comprehensive Cancer Centres can play a major role. Since the late 1980s (and even longer (IKZ)) the nine regional cancer registries have been gathering a wealth of information on the occurrence of cancer in the Dutch population, including tumour characteristics, diagnostics and treatment methods. Besides bringing out reports on the incidence of cancer and cancer mortality, population-based cancer registries in co-operation with tumour working groups can serve various purposes, e.g. mapping diagnostics, treatment and the course of disease after treatment (patterns of care), evaluating treatment guidelines and consequently helping to optimise curative treatment and care for oncological patients and to mould future-oriented health care policy.

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Appendices

Summary

At the end of the nineteen eighties and the beginning of the nineteen nineties, it was clear that very little knowledge was available on the course of cancer in elderly people, particularly on the specific treatment of elderly cancer patients. Existing data were mainly based on patients of younger than 70 years. Clinical trials often employed an even lower age limit. The scarcity of knowledge came to light because of increasing confrontation with elderly cancer patients and their specific problems. Existing data show that 45% of all cancer patients are 70 years or older at diagnosis. As this percentage can only be expected to rise owing to the progressive aging of the Dutch population, cancer in the elderly will attract increasing attention.

In this thesis, we look at age-specific differences in treatment and survival for various forms of cancer. Furthermore, we describe cancer incidence and mortality rates in the very elderly (85 years and older) in the Netherlands.

Chapter 2 describes a study on differences in diagnostics and treatment between younger and older patients with several common forms of cancer. Data on patients aged 50 years and older diagnosed in the period 1986-1992 with breast, colo-rectal, lung, ovarian, head and neck cancer and non-Hodgkin lymphoma were supplied by the Comprehensive Cancer Centre Limburg (n=6911).
In the patients with breast, lung and ovarian cancer, increasing age was associated with an increase in the percentage of patients without histological confirmation ($p<0.05$). In lung tumours, the percentage of cytological confirmations increased with age. The malignancy grade according to the Working Formulation had been made in fewer elderly patients with non-Hodgkin lymphoma than in younger patients. In all the forms of cancer addressed in this study, the percentage of patients who underwent extensive staging investigations decreased with increasing age (c-factor). At all the forms of cancer analysed, stage unknown at diagnosis was encountered more frequently in elderly patients than in younger patients. All these findings support the hypothesis that diagnostics are far less extensive in elderly patients than in younger patients.
Over 18% of the total study population had not been treated. In the 50-59 year old patients this was 7%, in the 60-69 year old patients 12% and in the 70 year and older category this was 22%. The percentages differed per form of cancer and varied from 9%, 9% and 16% untreated with breast cancer, to 38%, 58% and 74% untreated with non-small cell lung cancer per age category, respectively. Logistic regression analyses corrected for stage and sex also showed that the chance of not receiving treatment increased with age.
The vast majority of patients with breast cancer received treatment (99%). Elderly women tended to receive one treatment modality alone, whereas younger women received a combination of treatment modalities.

Chapter 3 not only addresses the influence of age on the choice of treatment in patients with ovarian cancer, but also age-specific differences in survival. Treatment data and information about vital status were analysed in 367 women with an epithelial form of ovarian cancer diagnosed in the period 1986-1992.

Patients with ovarian cancer stage I-II (n=112) were treated with surgery (0-54 years: 51%, 55-69 years: 35% and 70 years and older: 48%) or with surgery followed by chemotherapy (45%, 60% and 35% per age category, respectively). Two patients both older than 70 years did not receive treatment. The majority of patients with ovarian cancer stage III-IV (n=238) were treated with surgery + chemotherapy (the standard treatment), but the rates decreased with increasing age (71%, 54% and 37% per age category, respectively). A larger proportion of the elderly population received chemotherapy alone (22%, 28% and 37% per age category) or did not receive treatment (2%, 13% and 21% per age category).
In order to correct for death from competing causes, relative survival rates were calculated. Relative five year survival rates were 54%, 34% and 17% in the age categories 0-54 years, 55-69 years and 70 years and older, respectively. In patients with stage I-II at diagnosis, these rates were 86%, 66% and 51%, while in patients with stage III-IV these rates were 33%, 20% and 5% per age category. Even when the analyses were confined to patients who received surgery + chemotherapy (the standard treatment) the age effect remained.

Chapter 4 describes a similar study on cervical cancer, which generally has a better prognosis than ovarian cancer. The standard treatment for early stage cervical cancer was surgery; for more advanced stages, standard treatment comprised surgery followed by radiotherapy, or radiotherapy alone. In inoperable patients with early stage cancer, radiotherapy was also an accepted alternative.
The study was performed on data on 1176 patients who were diagnosed with cervical cancer in the period 1986-1996. Study follow-up ended on 1 January 1998.
Only 5% of the patients aged 70 years and older (n=224) were diagnosed with an early stage (IA). This percentage was 30% in patients of younger than 50 years (n=612) and 11% in the patients aged 50-69 years (n=340). Over 48% of the 70$^+$ age category patients with stage IB-IIA were treated with radiotherapy as the only treatment modality (<50 years: 8%; 50-69 years: 25%). The majority of patients with an advanced stage received radiotherapy alone: 70$^+$ years: 76%, 50-69 years: 86%; < 50 years: 72%. Over 10% of the 70$^+$ age category patients did not receive curative treatment (50-69 years: 5%; <50 years: 1.5%).
Five year relative survival in the total patient population was 69% (95% BI: 66%-72%) and differed per age category (<50 years: 81%; 50-69 years: 57%; 70$^+$ years: 49%) and per stage (FIGO stage IA: 97%; IB-IIA: 78%; IIB-IVA: 37%; and IVB: 14%).
Multivariate analyses on patients with stage IB-IVA who were treated with surgery, radiotherapy or both were performed to investigate the independent influence of age on relative survival. In this group of patients, stage and treatment rather than age were the most important prognostic factors. However, it is very probable that the influence of treatment was caused by the selection of patients for treatment on the basis of other factors, such as tumour size, comorbidity and performance status.

In the three studies described above, we did not include any information about accompanying diseases (comorbidity) or performance status (the general physical condition) of the patients. Both these factors might play a role in the choice of treatment. To perform the study described in Chapter 5, this information together with extensive data on treatment and pulmonary function were gathered by registration clerks from the IKL and IKO.
The study population comprised 803 patients diagnosed with non-small cell lung cancer in the period 1997-1998; 51% of the patients were 60-74 years of age and 27% were 75 years or older. After correcting for stage at diagnosis, analyses showed that the percentage of patients who were not treated according to the guideline increased with increasing age. Significant associations with comorbidity and performance status were only found in the patients with early stage disease. In stage IV patients, poor pulmonary function was associated with not receiving palliative treatment. Calendar age was found to be of decisive importance in the choice of treatment for patients with non-small cell lung cancer.

Chapter 6 analysed the incidence of mortality from cancer at a very advanced age (85^+ years). Due to aging of the population, this age group has steadily been increasing in size. In 1976, approximately 99,000 persons in the Netherlands were 85 years or older; in 1995, this number had increased to 203,000.
At present, the majority of cancer registries calculate incidence rates for the total group of 85^+, sometimes even for 65^+. The increased number of very elderly people has made it possible and much more relevant to distinguish between several age categories above the age of 85 years. In this study, we analysed the age categories 85-94 years and 95 years and older. Incidence data on all patients of 55 years and older in the Netherlands who were diagnosed in the period between 1989-1995 were made available by the Netherlands Cancer Registry (NKR). Population rates and causes of death were supplied by Statistics Netherlands (CBS).
In the period 1989-1995, a total of 27,633 persons aged 85 years and older were diagnosed with cancer. This was over 8% of the total number of patients (335,156). For all forms of cancer together, the age specific incidence reached a peak at the age of 85-94 years, after which it decreased. For lung cancer, the peak was reached as early as at the age of 75-84 years.
For nearly all the forms of cancer studied, mortality from cancer increased with increasing age. This did not apply to lung and pancreatic cancer in men and women, or to ovarian cancer in women.
The proportional mortality from cancer appeared to decrease with increasing age: in men and women aged 55-64 years, 42% and 52% died of cancer, whereas in men and women of older than 95 years, these rates were 11% and 7%, respectively.
Various explanations can be put forward for the finding that instead of increasing, the incidence decreased with advancing age. For example, under-reporting of cancer may have occurred in the very elderly because less extensive diagnostics were employed. However, this percentage cannot be all that large. The fact that the diagnosis was not confirmed microscopically as often in elderly patients leads to the assumption that although the diagnostic procedure was less extensive, a clinical diagnosis had been made.

A second possible explanation is that the very elderly had experienced less exposure to certain carcinogenic substances, e.g. because smoking had not yet become a general habit (cohort effect). It has also been suggested that the very elderly are less likely to develop cancer because they have strong genes that break down carcinogenic substances in the body.

This thesis is concluded with a general discussion in which the most important findings are summarized and elaborated on, based on current developments in the field of cancer in the elderly.
Over the past few years, increasing attention has been paid to the treatment of elderly cancer patients, both to surgical treatment and to radiotherapy and chemotherapy. Doctors and other health professionals agree in principle that even in patients of advanced age, these forms of treatment have a great deal to offer either with curative or palliative intent.
In addition, we postulate that the influence of calendar age on the choice of treatment partly is determined by the prognosis of the form of cancer in question, the nature and complexity of the treatment, possible risks of withholding treatment and by the attitudes and preferences of the treatment team.
A treatment approach according to protocol that has been tried, tested and approved in younger adults, may not be suitable for elderly patients without further considerations being made. One of the major characteristics of growing old is that people age at different rates, so there can be vast differences between elderly people. Therefore, age in itself, i.e. calendar age, is not a suitable criterion on which to select patients for a certain treatment. The differences between elderly people can be physical, social, psychological and functional; these aspects determine the biological age. This notion has led internationally to the insight that extensive geriatric assessment (Comprehensive Geriatric Assessment CGA), which is already being used for other disorders in the geriatric population, can probably make a positive contribution to the correct management of elderly cancer patients.
A treatment that deviates from the standard treatment or deviates from the guideline is not automatically an inferior treatment. When this treatment choice has been made after careful consideration of the different factors, then adaption of the treatment seems justified.

At the end of Chapter 7 a number of recommendations are made for further research and for clinical practice. For example, we argue in favour of introducing an extensive or less extensive geriatric assessment for elderly cancer patients to measure physical, cognitive and emotional functioning, comorbidity, nutritional level, family situation, personal preferences and medication use. It is also important to carefully document all the data so that evaluations can be made of the treatment applied. In the same way we argue in favour of setting up trials for elderly patients that also include cases with comorbidity or a poor performance status and to stimulate the participation of elderly patients in trials. Last but not least, attention is paid to the supporting role that the Comprehensive Cancer Centres can play in these processes.

Samenvatting

Eind jaren 80, begin jaren 90 van de vorige eeuw werd het duidelijk dat kennis over het verloop van kanker bij ouderen, maar vooral ook kennis over de specifieke behandeling van oudere kankerpatiënten nauwelijks voorhanden is. De aanwezige kennis over behandelingsmethoden is veelal gebaseerd op patiënten jonger dan zeventig jaar. Bij klinisch onderzoek wordt namelijk vaak deze of een nog lagere leeftijdsgrens aangehouden. De schaarste aan kennis komt aan het licht omdat men in toenemende mate geconfronteerd wordt met oudere kankerpatiënten en hun specifieke problematiek. Immers, 45% van alle kankerpatiënten is bij diagnose 70 jaar of ouder. Omdat dit percentage alleen nog maar kan toenemen gezien de voortschrijdende vergrijzing van de Nederlandse samenleving, komt *kanker bij ouderen* steeds meer in de belangstelling te staan.

In dit proefschrift wordt voor verschillende vormen van kanker gekeken naar leeftijdspecifieke verschillen in behandeling en overleving. Daarnaast wordt het vóórkomen van en de sterfte aan kanker onder de oudste ouderen (85 jaar en ouder) van Nederland beschreven.

In hoofdstuk 2 wordt het onderzoek naar verschillen in diagnostiek en behandeling tussen jongere en oudere kankerpatiënten voor enkele veel voorkomende vormen van kanker beschreven. Gegevens van patiënten in de leeftijd van 50 jaar en ouder, gediagnosticeerd in de periode 1986-1992 met borst-, dikke darm/endeldarm-, long-, eierstok- en hoofdhalskanker en het non-Hodgkin lymfoom werden verstrekt door de kankerregistratie van het Integraal Kankercentrum Limburg (N=6911).
Wat betreft diagnostiek werd bij patiënten met borst-, long- en eierstokkanker met het stijgen van de leeftijd een duidelijke toename van het percentage patiënten zonder histologische bevestiging gesignaleerd ($p<0.05$). Bij longtumoren nam het percentage cytologische bevestiging toe met de leeftijd. Voor het non-Hodgkin lymfoom gold dat de maligniteitsgraad volgens de Working Formulation vaker niet geclassificeerd was bij ouderen dan bij jongeren. Bij alle bestudeerde vormen van kanker steeg het percentage patiënten waarbij minder uitgebreid stadiëringsonderzoek had plaatsgevonden met de leeftijd (c-factor). Voor alle bestudeerde vormen van kanker werd gevonden dat het stadium waarin de ziekte zich bevond bij diagnose vaker onbekend was bij ouderen dan bij jongeren. Al deze bevindingen ondersteunen de hypothese dat ouderen minder intensief werden gediagnosticeerd dan jongeren.
Ruim 18% van de gehele onderzoekspopulatie werd niet behandeld. Van de 50-59 jarigen was dit 7%, van de 60-69 jarigen 12% en van de patiënten 70 jaar en ouder 22%. De percentages verschilden echter nogal per vorm van kanker, variërend van respectievelijk 9%, 9% en 16% niet-behandelde patiënten per leeftijdscategorie bij borstkanker tot 38%, 58% en 74% niet-behandelde patiënten met een niet-kleincellig longcarcinoom. Ook uit de de logistische regressie bleek dat, gecorrigeerd voor stadium en geslacht, de kans om niet te worden behandeld toenam met de leeftijd.
Patiënten met borstkanker werden bijna allemaal behandeld (99%), oudere vrouwen kregen echter vaker alléén hormonale therapie, terwijl jongere vrouwen werden behandeld met een combinatie van behandelingsmodaliteiten.

In hoofdstuk 3 wordt niet alleen de invloed van leeftijd op de keuze van behandeling voor patiënten met eierstokkanker nader bekeken, maar worden ook leeftijdspecifieke verschillen in overleving bestudeerd. Van 367 vrouwen met een epitheliale vorm van eierstokkanker, gediagnosticeerd in de periode 1986-1992 werden behandelingsgegevens en informatie over de vitale status geanalyseerd.
Patiënten met eierstokkanker stadium I-II (n=112) werden behandeld met chirurgie (0-54 jaar: 51%, 55-69 jaar: 35% en 70 jaar en ouder: 48%) of met chirurgie gevolgd door chemotherapie (45%, 60% en 35% per leeftijdsgroep). Twee patiënten, beiden ouder dan 70 jaar werden niet behandeld. Patiënten met eierstokkanker stadium III-IV (n=238) werden grotendeels behandeld met chirurgie+chemotherapie (de standaardbehandeling), maar dit percentage daalde naarmate de leeftijd steeg (71%, 54% en 37% per leeftijdsgroep). Ouderen werden vaker behandeld met chemotherapie alleen (22%, 28%, 37% per leeftijdsgroep) en werden ook vaker niet behandeld (2%, 13% en 21% per leeftijdsgroep).
Teneinde te corrigeren voor de 'normale' sterftekans werden relatieve overlevingscijfers berekend. De relatieve vijfjaarsoverleving bedroeg respectievelijk 54%, 34% en 17% voor de leeftijdsgroepen 0-54 jaar, 55-69 jaar en 70 jaar en ouder. Voor patiënten met stadium I-II bij diagnose waren deze percentages respectievelijk 86%, 66% en 51% en voor patiënten met stadium III-IV 33%, 20% en 5% per leeftijdsgroep. Ook wanneer louter patiënten behandeld met chirurgie+chemotherapie (de standaardbehandeling) in de analyse werden opgenomen bleef het effect van leeftijd bestaan.

In hoofdstuk 4 wordt een vergelijkbare studie beschreven, maar dan voor baarmoederhalskanker, een vorm van kanker met een over het algemeen betere prognose dan eierstokkanker. Standaardbehandeling voor baarmoederhalskanker in een vroeg stadium is chirurgie en in een verder gevorderd stadium chirurgie gevolgd door radiotherapie of radiotherapie alleen. Voor patiënten die niet geopereerd kunnen worden is radiotherapie ook in een vroeg stadium een geaccepteerd alternatief.
De studie was gebaseerd op de gegevens van 1176 patiënten bij wie een invasief cervixcarcinoom was vastgesteld in de periode 1986-1996. Einddatum van follow-up was 1 januari 1998.
Slechts 5% van de patiënten van 70 jaar en ouder (n=224) werd gediagnosticeerd met een vroeg stadium (IA). Dit percentage was 30% bij de vrouwen jonger dan 50 jaar (n=612) en 11% bij vrouwen in de leeftijdsgroep 50-69 jaar (n=340). Ruim 48% van de 70^+ patiënten met een stadium IB-IIA werd behandeld met radiotherapie als enige behandelingsvorm (< 50 jaar: 8%; 50-69 jaar: 25%). De meeste patiënten met een gevorderd stadium (IIB >) werden behandeld met alleen radiotherapie: 70^+ jaar: 76%, 50-69 jaar: 86%; < 50 jaar: 72%. Ruim 10% van de 70^+ vrouwen werd niet curatief behandeld (50-69 jaar: 5%; < 50 jaar: 1,5%).
De vijf-jaars relatieve overleving van de gehele patiëntenpopulatie was 69% (95% BI: 66%-72%) en verschilde per leeftijdsgroep (<50 jaar: 81%; 50-69 jaar: 57%; 70^+ jaar: 49%) en per stadium (FIGO-stadium IA: 97%; IB-IIA: 78%; IIB-IVA: 37%; IVB: 14%).
Middels multivariate regressie werd voor patiënten met een stadium IB-IVA, behandeld met chirurgie, radiotherapie of beiden, gekeken naar de onafhankelijke invloed van leeftijd op de relatieve overleving. Het bleek dat voor deze groep patiënten niet leeftijd maar stadium en behandeling de belangrijkste prognostische factoren waren.

Het is hierbij zeer waarschijnlijk dat de invloed van de behandeling in feite werd veroorzaakt door een selectie van patiënten voor behandeling op basis van andere factoren zoals tumorgrootte, co-morbiditeit en performance status.

In de drie voorgaande studies hadden we geen informatie over bijkomende ziekten (co-morbiditeit) en over de performance status (de algemene fysieke conditie) van patiënten. Dit zijn beide factoren die mede de behandelingskeuze kunnen bepalen. Voor de studie beschreven in hoofdstuk 5 werd deze informatie tezamen met uitgebreide behandelingsgegevens en de longfunctie door de registratiemedewerkers van het IKL en IKO verzameld. Het betrof 803 patiënten gediagnosticeerd met niet-kleincellig longkanker in de periode 1997-1998. Van deze patiënten was 51% in de leeftijd van 60-74 jaar en 27% was 75 jaar of ouder. Het bleek dat, rekening houdend met het stadium bij diagnose, het percentage patiënten dat niet behandeld werd volgens de richtlijn toenam met de leeftijd. Alleen bij de vroege stadia werd een verband met aanwezige co-morbiditeit en performance status gevonden. Bij stadium IV patiënten werd een verband gevonden tussen een slechte longfunctie en het niet ontvangen van palliatieve behandeling. Kalenderleeftijd bleek van doorslaggevende betekenis te zijn bij de therapiekeuze voor patiënten met een niet-kleincellige longtumor.

In Hoofdstuk 6 wordt de incidentie van en sterfte aan kanker op zeer hoge leeftijd (85^+) beschreven. Door de vergrijzing van de bevolking neemt deze leeftijdsgroep sterk toe in aantal. Waren er in 1976 99.000 personen in Nederland 85 jaar of ouder, in 1995 was dit aantal gestegen tot 203.000.
Tot nu toe berekenen de meeste kankerregistraties incidentiecijfers voor de totale groep van 85-plussers, soms zelfs voor 65^+. Het toegenomen aantal oudste ouderen maakt het echter mogelijk en relevanter ook boven de leeftijd van 85 jaar meerdere leeftijdsgroepen te onderscheiden. Voor onderhavige studie waren dit de categorieën 85-94 jaar en 95 jaar en ouder. Incidentie gegevens van alle patiënten van 55 jaar en ouder in Nederland, gediagnosticeerd in de periode 1989-1995 werden ter beschikking gesteld door de Nederlands Kankerregistratie (NKR). Bevolkingsaantallen en doodsoorzaken werden verstrekt door het Centraal Bureau voor de Statistiek.
In totaal werd in de periode 1989-1995 bij 27.633 personen van 85 jaar en ouder kanker gediagnosticeerd. Dit was ruim 8% van het totale aantal patiënten (335.156). Voor alle vormen van kanker samen bereikte de leeftijdspecifieke incidentie een piek op de leeftijd van 85-94 jaar waarna de incidentie weer daalde. Voor longkanker werd de piek al bereikt bij patiënten van 75-84 jaar.
Voor bijna alle bestudeerde vormen van kanker steeg de sterfte aan kanker met het stijgen van de leeftijd. Dit gold niet voor long- en alvleesklierkanker bij mannen en vrouwen en niet voor eierstokkanker bij vrouwen.
De proportionele sterfte aan kanker bleek bij het ouder worden af te nemen: bij mannen en vrouwen van 55-64 jaar stierf 42% en 52% aan kanker, maar bij mannen en vrouwen ouder dan 95 jaar waren deze percentages respectievelijk 11% en 7%.
Verschillende verklaringen worden aangedragen voor de bevinding dat de incidentie in plaats van te blijven stijgen, op hoge leeftijd weer daalde. Zo zou er sprake kunnen zijn van een onderrapportage van kanker bij de oudste ouderen doordat minder diagnostiek wordt verricht. Dit percentage kan echter nooit heel groot zijn.

Het feit dat de diagnose bij ouderen minder vaak microscopisch bevestigd is, doet vermoeden dat ofschoon minder uitgebreid, de klinische diagnose wel gesteld wordt. Een tweede mogelijke verklaring is dat de oudste ouderen minder blootgesteld zijn aan bepaalde kankerverwekkende stoffen, bijvoorbeeld omdat roken nog geen algemeen gebruik was (cohorteffect). Ook wordt wel gesuggereerd dat oudste ouderen minder vaak kanker ontwikkelen doordat zij beschikken over sterke genen om kankerverwekkende stoffen in het lichaam af te breken.

Het proefschrift wordt afgesloten met een algemene discussie waarin de belangrijkste bevindingen worden samengevat en toegelicht aan de hand van huidige ontwikkelingen op gebied van kanker bij ouderen.
Zowel bij de chirurgische behandeling van kanker als voor de radiotherapie en chemotherapie wordt de laatste jaren een toegenomen aandacht voor de behandeling van de oudere kankerpatiënt geconstateerd. Artsen en andere behandelaars zijn het er in principe over eens dat ook op oudere leeftijd deze behandelingsvormen hetzij curatief, hetzij palliatief, veel te bieden kunnen hebben.
Daarnaast wordt betoogd dat de invloed van de kalenderleeftijd op de behandelingskeuze mede bepaald wordt door de prognose van de betreffende vorm van kanker, de aard en gecompliceerdheid van de behandeling, eventuele risico's van het nalaten van een behandeling en door de houding en voorkeuren van de behandelaars.
Een protocollaire aanpak zoals die bij jongere volwassenen gebruikelijk en beproefd is, is niet zonder meer geschikt voor ouderen. Een van de belangrijkste kenmerken van het ouder worden is namelijk dat mensen onderling meer gaan verschillen. Daarom is leeftijd op zich, de 'kalender-leeftijd' geen geschikt criterium om mensen te selecteren voor een bepaalde behandeling. De verschillen tussen de ouder wordende mensen die niet alleen lichamelijk, maar ook sociaal, psychisch en functioneel kunnen zijn bepalen de biologische leeftijd. Dit besef heeft internationaal geleid tot het inzicht dat een uitgebreide geriatrische beoordeling (Comprehensive Geriatric Assessment CGA) zoals reeds gebruikt bij andere ziektebeelden in de geriatrische populatie, wellicht een positieve bijdrage kan leveren aan het op juiste wijze behandelen van de oudere kankerpatiënt.
Een behandeling die afwijkt van de standaard, of niet behandelen volgens de richtlijn, betekent niet automatisch een inferieure behandeling. Wanneer deze behandelingskeuze tot stand komt na zorgvuldige afweging van de verschillende factoren, lijkt een aanpassing van de behandeling gerechtvaardigd.

Aan het eind van hoofdstuk 7 wordt een aantal aanbevelingen gedaan voor verder onderzoek en voor de klinische praktijk. Onder meer wordt gepleit voor de invoering van een meer of minder uitgebreide geriatrische beoordeling van oudere kankerpatiënten op gebied van fysiek, cognitief en emotioneel functioneren, co-morbiditeit, voedingstoestand, gezinssituatie, eigen wensen en medicijngebruik. Belangrijk hierbij is zorgvuldige documentatie van de gegevens, zodat evaluatie van de gegeven behandeling kan plaatsvinden. Eveneens wordt gepleit voor het opzetten van trials voor oudere patiënten, ook voor hen met co-morbiditeit of een slechte performance status en voor het stimuleren van deelname van oudere patiënten aan trials. Tenslotte wordt aandacht geschonken aan de ondersteunende rol die de Integrale Kankercentra hierbij kunnen spelen.

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Semra en Ismet, jullie stonden altijd al op de eerste plaats, en dat blijft zo.

Curriculum Vitae

Marjan de Rijke werd geboren op 22 september 1961 te Middelburg. In 1979 behaalde zij het Atheneum-A diploma aan de Christelijke Scholengemeenschap Walcheren, eveneens te Middelburg. In datzelfde jaar begon zij in Vlissingen aan de inservice opleiding voor A-verpleegkundige. Na het behalen van haar diploma in 1983 werkte zij nog twee jaar in hetzelfde ziekenhuis als gediplomeerd verpleegkundige op de afdeling urologie/ orthopedie /oogheelkunde. In 1985 verhuisde zij naar een noordelijker gelegen eiland (Schouwen-Duiveland) en werkte aldaar in het kleine streekziekenhuis te Zierikzee op de afdeling chirurgie/gynaecologie. In 1989 vond zij het tijd voor een rigoreuze verandering en vertrok zij naar Maastricht om haar heil te zoeken in de wetenschap. Van 1989 tot 1993 studeerde zij daar met veel plezier Gezondheidswetenschappen aan de Universiteit Maastricht, afstudeerrichting Theorie van de Gezondheidswetenschappen. Teneinde ook op het gebied van onderzoek zo breed mogelijk onderlegd te geraken, volgde zij in 1995 de Postdoctorale opleiding Epidemiologie van het EMGO aan de Vrije Universiteit te Amsterdam. Onderdeel van deze opleiding was een onderzoeksstage, welke zij verricht heeft op de afdeling Kankerregistratie en Epidemiologie van het Integraal Kankercentrum Limburg (IKL) te Maastricht. Na het behalen van het diploma werd zij in 1996 aangesteld als projectmedewerker op deze afdeling. Dit is zij blijven doen tot 1 oktober 2002. Sinds die datum werkt zij als onderzoeker op het Pijn Kennis Centrum in het academisch ziekenhuis Maastricht. Post-operatieve pijn en pijn bij kankerpatiënten zijn hier de aandachtsgebieden waarop zij werkzaam is.